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HCV NS-3 Serine Protease Inhibitors

Technical Field

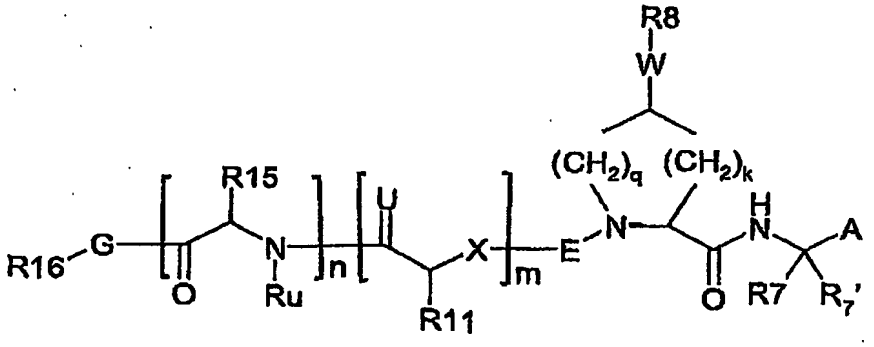
This invention relates to novel inhibitors of the NS3 serine protease of the flavivirus HCV and to methods for their use in the treatment or prophylaxis of HCV.

Background Art

The NS3 serine protease of HCV is a multifunctional protein which contains a serine protease domain and a RNA helicase domain. The protease cofactor NS4A, which is a relatively small protein, is absolutely required for enhanced serine protease activity. The NS3 serine protease is essential in the viral lifecycle. From analysis of the substrate binding site as revealed by X-ray crystal structure, it has been shown that the binding site of the NS3 protease is remarkably shallow and solvent exposed making small molecule inhibitor design a challenge.

Brief description of the invention

In accordance with a first aspect of the invention, there are provided compounds of the formula I:



wherein

A is $COOR^1$, $CONHSO_2R^2$, $CONHR^3$, or $CR^4R^{4'}$ wherein;

R^1 is hydrogen, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^2 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^3 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, -OC_1-C_6alkyl, -OC_0-C_3alkylcarbocyclyl, -OC_0-C_3alkylheterocyclyl;

R^4 is =O, halo, amino, or OH;

$R^{4'}$ is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl; wherein

R^2, R^3, and R4' are each optionally substituted with from 1 to 3 times with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p R_b$, Y-S(=O)$_p R_b$, Y-S(=O)$_p$NRaR_b, Y-C(=O)OR_b, Y-NRaC(=O)OR_b;

where Y is a bond or C_1-C_3 alkyl;

Ra is H or C_1-C_3 alkyl;

Rb is H or C_1-C_6 alkyl;

p is 1 or 2;

R^7 is C_1-C_6alkyl, C_1-C_3alkyl C_3-C_7cycloalkyl, or C_2-C_6alkenyl, any of which is optionally substituted with 1-3 halo atoms, amino or –SH;

$R^{7'}$ is H or taken together with R^7 to form a C_3-C_6 cycloalkyl ring optionally substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is C_1-C_6 alkyl, C_3-C_5cycloalkyl, C_2-C_6 alkenyl or J; any of which may be optionally substituted with halo;

q is 0 to 3 and k is 0 to 3; where $q+k \geq 1$;

W is -CH_2-, -O-, -OC(=O)NH-, -OC(=O)-, -S-, –NH-, -$NR^{8'}$, -$NHSO_2$- or -NHC(=O)-;

R^8 is a ring system containing 1 or 2 saturated or unsaturated rings each of which has 4-7 ring atoms and 0 to 2 hetero atoms selected from S, O and N, the ring system being optionally spaced from W by a C_1-C_3 alkyl group; or R^8 is C_1-C_6 alkyl, any of which R^8 groups can be optionally mono, di, or tri substituted with R^9, wherein

R^9 is independently halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p R_b$, Y-S(=O)$_p R_b$, Y-S(=O)$_p$NRaR_b, Y-C(=O)OR_b, Y-NRaC(=O)OR_b; wherein the carbocyclyl or heterocyclyl is optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di- substituted with C_1-C_6-alkyl, sulfonyl, (C_1-C_3 alkyl)sulfonyl, NO_2, OH, SH, halo, haloalkyl, carboxyl, amide, (C_1-C_3alkyl)amide, or heteroaryl optionally substituted with C_1-C_6alkyl;

$R^{8'}$ is H, C_1-C_3 alkyl;

E is -C(=O)-, -C(=S)-, -$S(=O)_2$-, -S=O-, -C=N-Rf;

Rf is H, -CN, -C(=O)NRaRb; -C(=O)C_1-C_3 alkyl

X is –NRx- where Rx is H, or C_1-C_6alkyl; or in the case where where E is –(C=O)- X can also be –O-;

R^{11} is H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p$$R_b$, Y-S(=O)$_p$$R_b$, Y-S(=O)$_pNRaR_b$, Y-C(=O)O$R_b$, Y-NRaC(=O)O$R_b$;

when $R^{7'}$ taken together with R^7 forms a C_3-C_6 cycloalkyl, then one of Rx or R^{11} can also be J;

J is a 3 to 10-membered saturated or unsaturated alkylene chain extending from the R^7/$R^{7'}$ cycloalkyl to Rx or R^{11} to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -NR^{12}- wherein 0 to 3 carbon atoms in the chain are optionally substituted with R^{14}; wherein;

R^{12} is H, C_1-C_6 alkyl, C_3-C_6cycloalkyl, or COR^{13};

R^{13} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^{14} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, halo, amino, oxo, thio, or C_1-C_6 thioalkyl;

Ru and Rz are independently H or C_1-C_3 alkyl;

m is 0 or 1; n is 0 or 1;

U is =O or is absent;

R^{15} is H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylheteroaryl, C_0-C_3alkylcycloC_3-C_6alkyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-

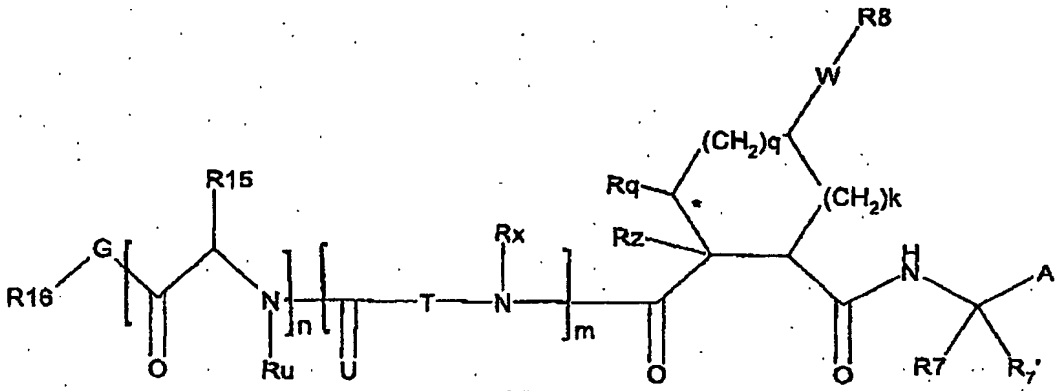
$C(=O)R_b$, Y-$(C=O)NRaR_b$, Y-$NRaC(=O)R_b$, Y-$NHSO_pR_b$, Y-$S(=O)_pR_b$, Y-$S(=O)_pNRaR_b$, Y-$C(=O)OR_b$, Y-$NRaC(=O)OR_b$;

G is –O-, -NRy- or –NHNH- where Ry is H or C_1-C_3 alkyl;

R^{16} is H; or C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-$NHSO_pRb$, Y-$S(=O)_pRb$, Y-$S(=O)_pNRaRb$, Y-C(=O)ORb, Y-NRaC(=O)ORb;

or a pharmaceutically acceptable salt or prodrug thereof.

A second aspect of the invention provides compounds of the formula VI:



VI

wherein

R^7, $R^{7'}$, R^8, R^{11}, R^{15}, R^{16}, Rx, Ru, A, G, k, m, n, U are as defined above;

q' is 0 or 1;

Rz is H, or together with the asterisked carbon forms an olefinic bond;

Rq is H or C_1-C_4-alkyl;

T is $-CHR^{11}$- or –NRd-, where Rd is H or C_1-C_3alkyl;

in the case where R^7 taken together with $R^{7'}$ forms a C_3-C_6 cycloalkyl, one of Rx, Rd or R^{11} can be J;

J is a 5 to 10 membered saturated or unsaturated alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rx, Rd or R^{11} to form a macrocycle, which chain is otherwise as defined above;
and pharmaceutically acceptable salts and prodrugs thereof.

Without in any way wishing to be bound by theory, or the ascription of tentative binding modes for specific variables, P1, P2, P3 and P4 as used herein are provided for convenience only and have their conventional meanings and denote those portions of the inhibitor believed to fill the S1, S2, S3 and S4 subsites respectively of the enzyme, where S1 is adjacent the cleavage site and S4 remote from the cleavage site.

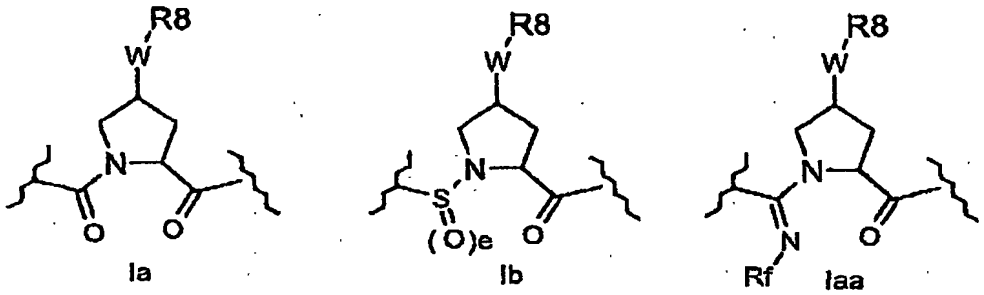
The compounds of the present invention, as embodied in formula I and VI can be briefly represented as R^{16}-G-P4-P3-link-P2-P1, wherein P3 and/or P4 may be absent, and P1, P3 and P4 each represents a building block constituted of a derivative of a natural or unnatural amino acid, P2 is a cyclic residue and G and R^{16} are as defined for formula I and VI. The link is a carbonyl or other function as defined for E. The P1 and P2 building blocks and the P3 and P4 building blocks are thus linked together by amide bonds whereas the P2 and P3 building blocks are linked through the above described link. The amide bonds are thereby reversed relative to each other on each side of the link in the compounds according to formula (I) and (VI).

Additional aspects of the invention include a pharmaceutical composition comprising a compound of Formula I or VI as defined above and a pharmaceutically acceptable carrier or diluent therefore.

The compounds and compositions of the invention have utility in methods of medical treatment or prophylaxis of HCV infections in humans. Accordingly, a further aspect of the invention is the use of a compound as defined above in the manufacture of a

medicament for the prophylaxis or treatment of flavivirus infections in humans or animals. Exemplary flavivirus include BVDV, dengue and especially HCV.

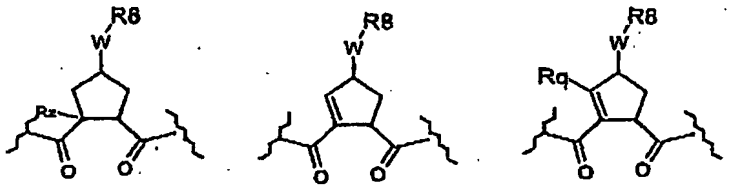
Preferred values for q and k in Formula I include 1:2, 2:1, 2:3, 3:2, 3:3, more preferably 2:2; and most preferably 1:1, in which case preferred compounds have the partial structure:



where e is 1 or 2.

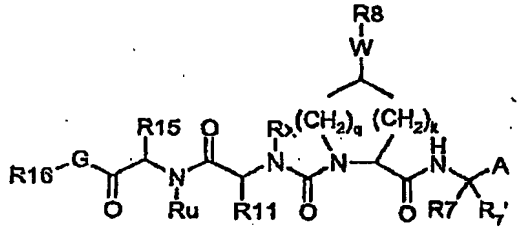
It is currently preferred that E is –C(=O)- or –C=N-Rf, for example where Rf is -CN or-C(=O)NH_2

Preferred values for q' and k in formula VI include 0:2, 1:1, 1:3, 2:2, 2:3, more preferably 1:2; and most preferably 0:1, in which case preferred compounds have one of the partial structures:

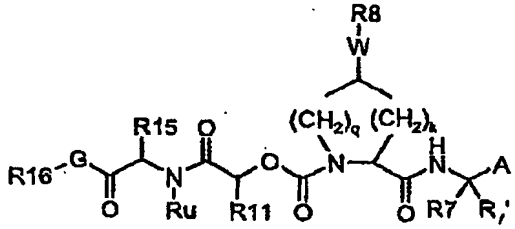


especially where Rz is H or Rq is H or methyl.

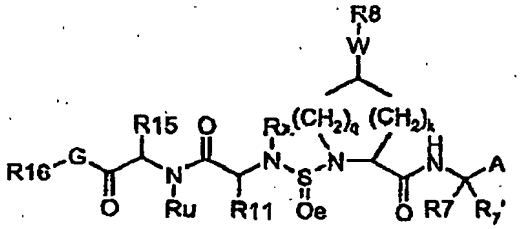
Compounds of formula I and VI may comprise both a P3 and a P4 function, viz m and n are each 1. These embodiments of the invention thus have the formulae IIId-IIIfa for formula I, and VIIIc and VIIId for formula VI



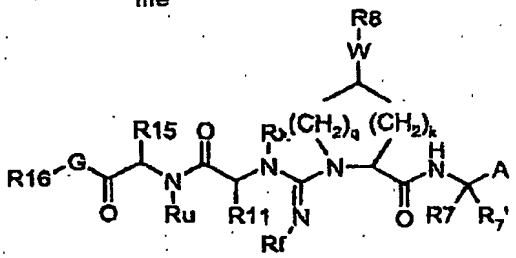
IIId



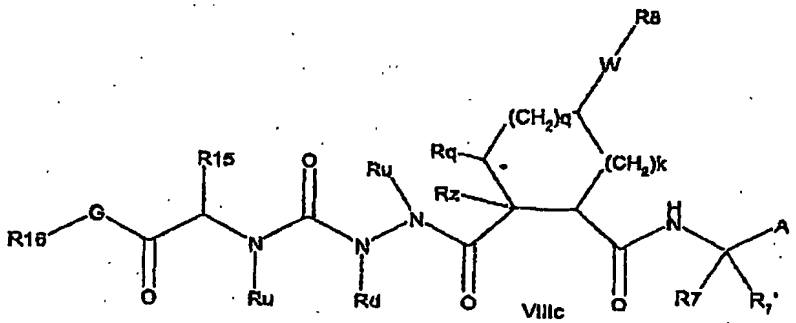
IIIe



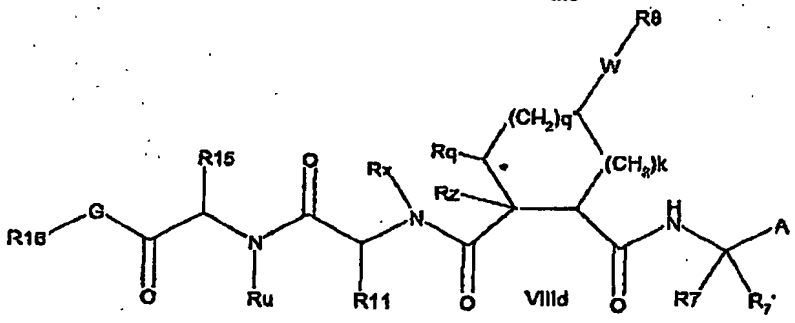
IIIf



IIIfa

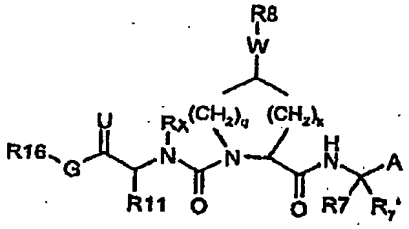


VIIIc

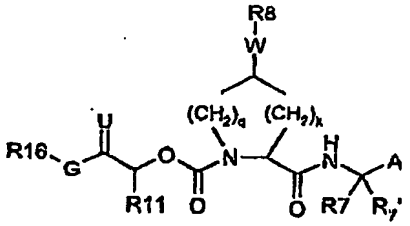


VIIId

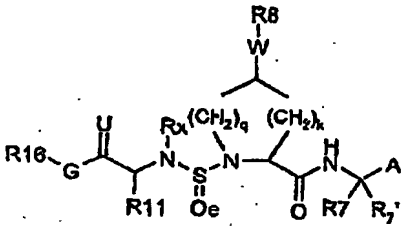
Alternative configurations of Formula I and VI comprise a P3, but no P4 function, viz m is 1 and n is zero. Preferred embodiments with this configuration include Formulae IIa- IIc within Formula I and Formulae VIIa and VIIb in Formula VI.



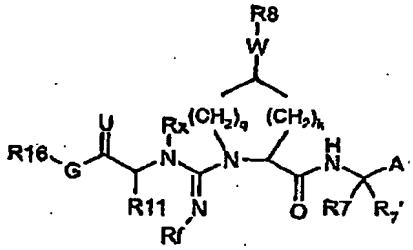
IIa



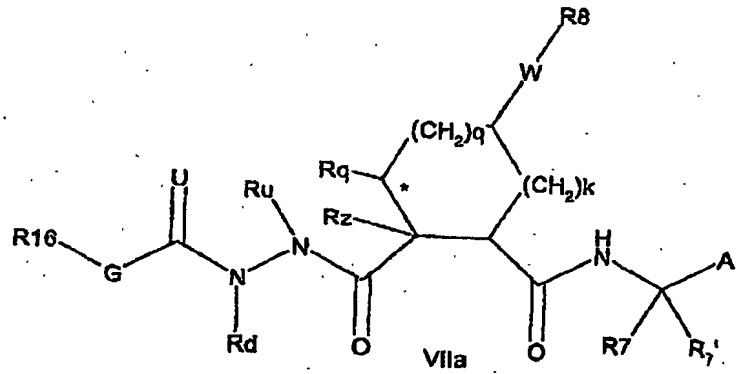
IIb



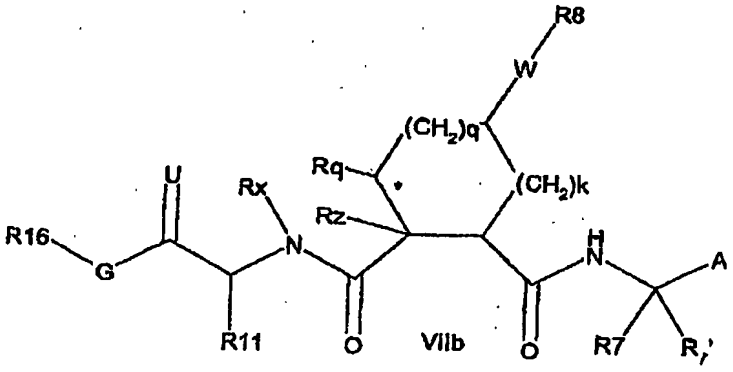
IIc



IIaa



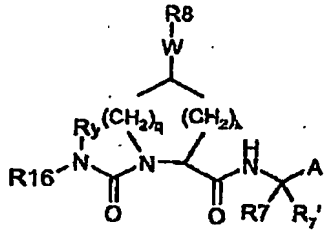
VIIa



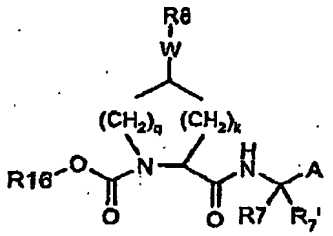
VIIb

Still further alternative configurations of the compounds of Formulae I and VI include those where m and n are zero and thus groups R^{16}-G abut P2. Embodiments within

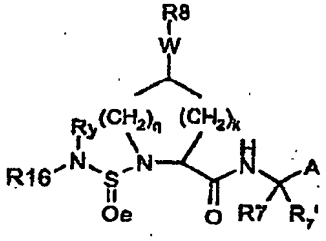
this alternative include Formulae IIIa-IIIc within Formula I and Formula VIII within Formula VI:



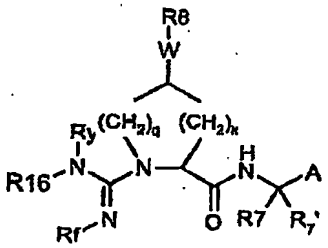
IIIa



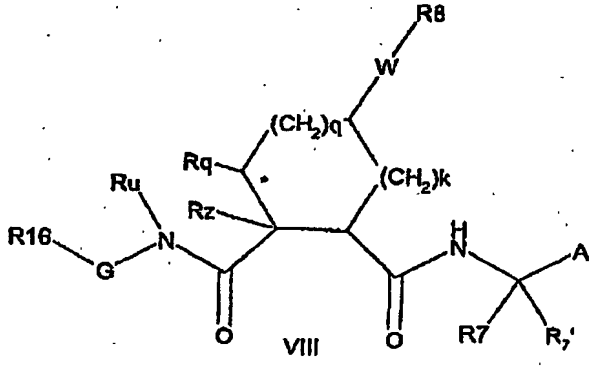
IIIb



IIIc



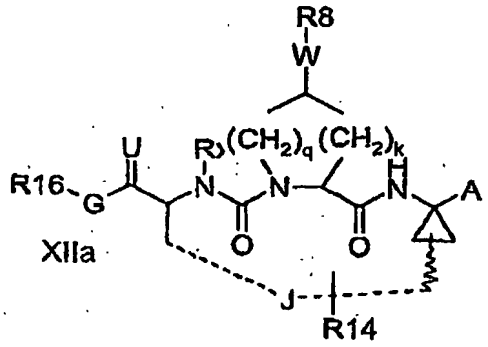
IIIaa



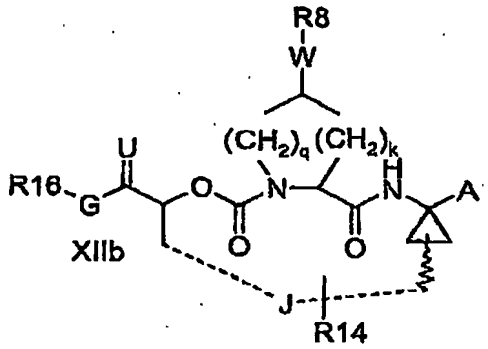
VIII

The compounds of the invention may comprise linear molecules, as depicted above. Alternatively, in embodiments wherein R^7 and $R^{7'}$ together define a spiro cycloalkyl group, such as spiro-cyclopropyl, the compounds of the invention may be configured as macrocycles, wherein a linking group J extends between Rx or R^{11} of formula I or Rx, Rd or R^{11} of Formula VI.

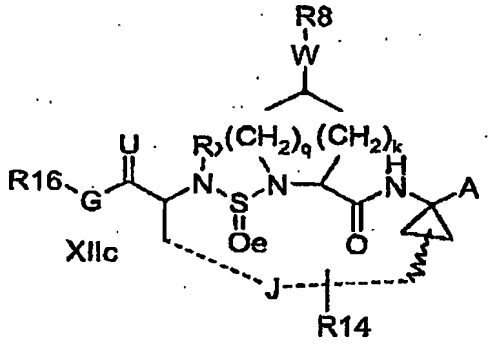
Embodiments of such macrocyclic structures within formula I with various permutations of P3 and P4 include Formulae XIIa-XIIc, XIIg-XIII and XIIIa and XIIIb.



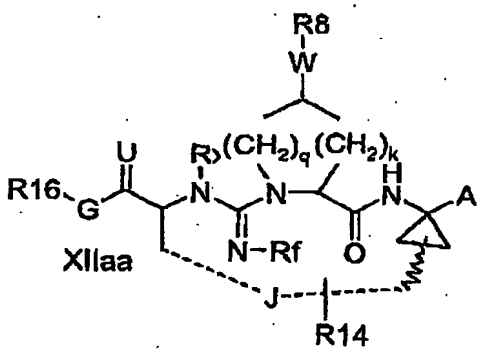
XIIa



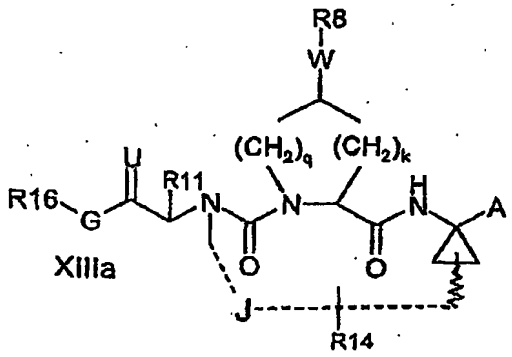
XIIb



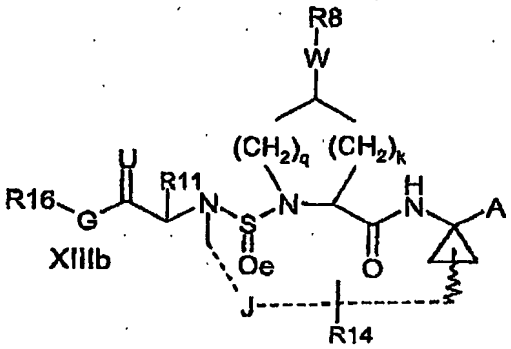
XIIc



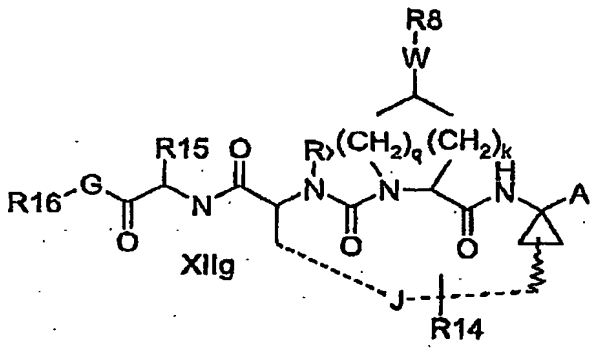
XIIaa

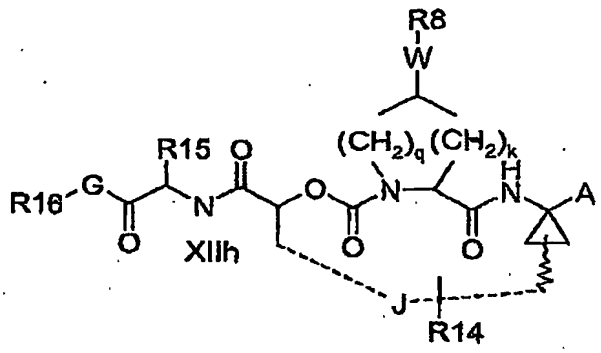


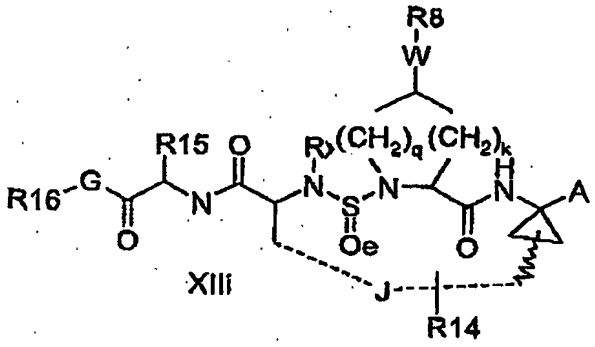
XIIIa

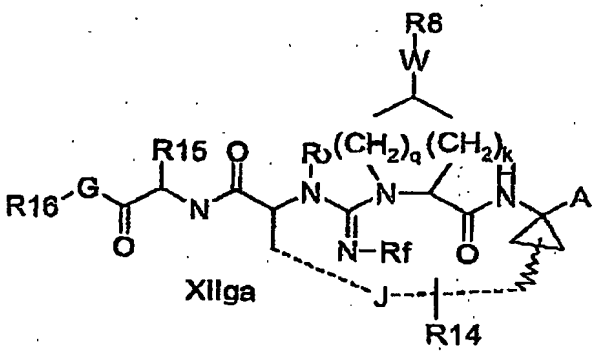


XIIIb

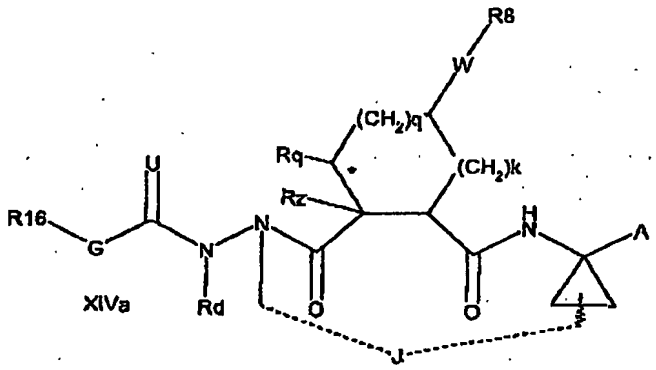


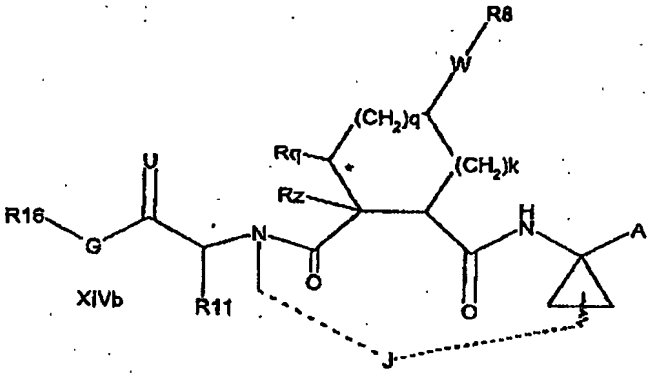


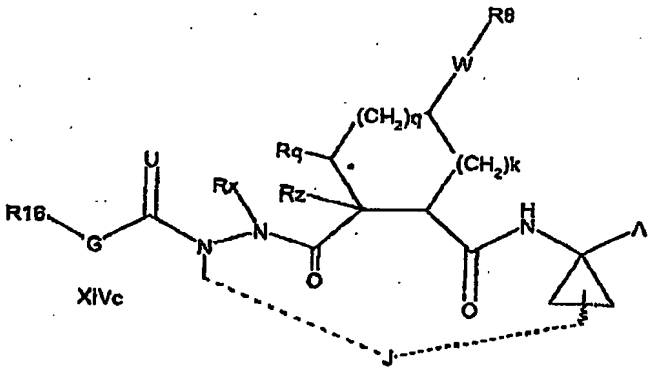


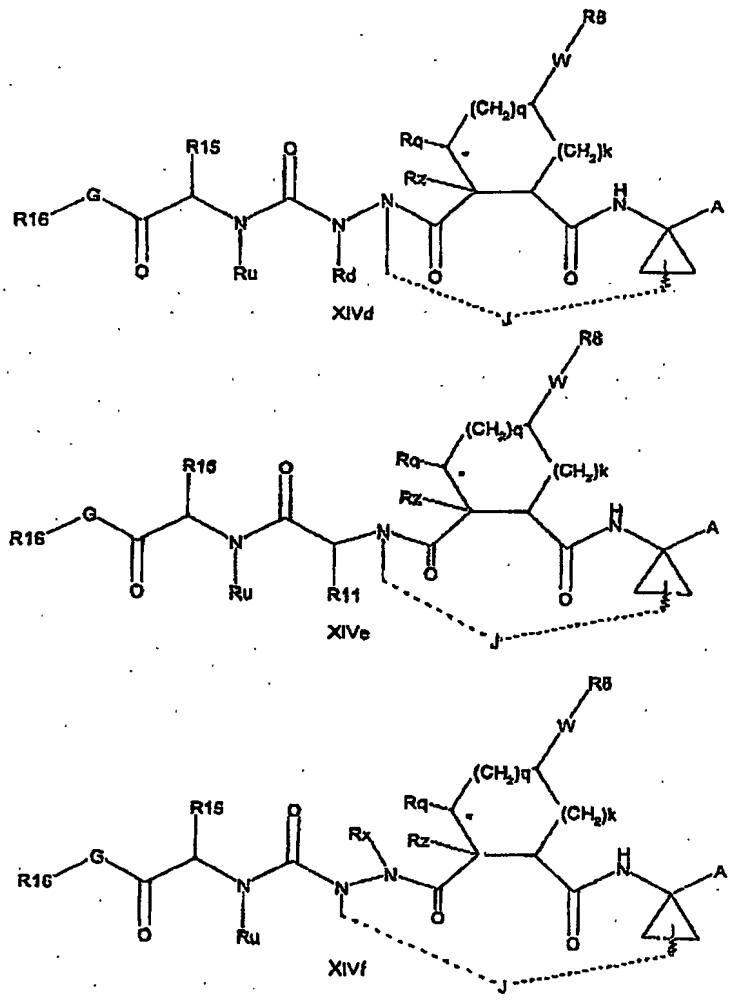


Embodiments of such macrocyclic structures within formula VI with various permutations of P3 and P4 include Formulae XIVa-XIVf:









In general linker J, where present, is a 3 to 10 chain atom, preferably 5 to 8 atom, such as 6 or 7 atom, saturated or unsaturated alkylene chain. The length of the chain will, of course, depend on whether J extends form Rd, Rx, or R^{11}. Suitable chains are described in detail in WO 00/59929.

Conveniently, the J chain contains one or two heteroatoms selected from: O, S, NH, NC_1-C_6 alkyl or N-C(=O)C_1-C_6alkyl. More preferably, the J chain optionally contains one heteroatom selected from: NH, or N-C(=O)C_1-C_6alkyl, most preferably N(Ac). Most preferably, the chain containing a nitrogen atom is saturated. Alternatively, J contains one heteroatom selected from: 0, or S. Preferably, this chain is substituted

with R^{14}, such H or methyl. Even more preferably, J is saturated.

Alternatively, J contains a double bond, typically spaced one carbon from the cycloalkyl R^7 function. The double bond may be cis or trans.

Representative examples of J thus include pentanyl, hexanyl, heptanyl, any of which are substituted with C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxyl, halo, amino, oxo, thio or C_1-C_6 thioalkyl; penten:3:yl, hexen:4:yl, hepten:5 yl, where 3, 4 or 5 refers to a double bond between 3 carbon atoms 3 and 4, 4 and 5 etc.

Convenient R^7 and $R^{7'}$ groups include those wherein $R^{7'}$ is H and R^7 is n-ethyl, n-propyl, cyclopropylmethyl, cyclobutylmethyl, 2,2-difluoroethyl, or mercaptomethyl. Preferred embodiments include those wherein R^7 is n-propyl or 2,2-difluoroethyl.

Alternatively, R^7 and $R^{7'}$ together define a spiro-cycloalkyl function, such as a spiro-cyclobutyl ring, and more preferably a spiro-cyclopropyl ring. The ring is substituted or unsubstituted. Preferred substituents include mono or di-substitutions with R^{7a} wherein R^{7a} is C_1-C_6 alkyl, C3-C5cycloalkyl, or C_2-C_6 alkenyl, any of which is optionally substituted with halo. Alternatively the substituent may be a J linker as described above.

Particularly preferred substituents include R^{7a} as ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl. Currently preferred stereochemistries for a spiro-cyclopropyl ring are defined below.

A favoured configuration for A is $-CR^4R^{4'}$ as illustrated in detail in PCT/EP03/10595, the contents of which are incorporated by reference.

Convenient R^4 groups thus include C_1-C_6alkyl, such as methyl, ethyl, propyl, ethenyl and $-CHCHCH_3$. Alternative preferred R^4 groups include aryl or heteroaryl such as optionally substituted phenyl, pyridyl, thiazolyl or benzimidazolyl or C_1-C_3alkylaryl or C_1-C_3alkylheteroaryl, where the alkyl moiety is methyl, ethyl, propyl, ethenyl and –

$CHCHCH_3$. Preferred aryl moieties include optionally substituted phenyl, benzothiazole and benzimidazole.

Favoured $R^{4'}$ groups include $-NH_2$, fluoro or chloro. Alternative preferred R4' groups include --OH and especially =O.

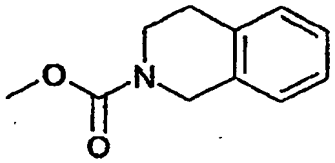
An alternative favoured configuration for A is $CONHR^3$, where R^3 is optionally substituted C_0-C_3alkylaryl, C_0-C_3alkylhetroaryl, OC_0-C_3alkylaryl or OC_0-C_3alkylhetroaryl.

An alternative favoured configuration for A is $CONHSO_2R^2$, especially where R^2 is optionally substituted C_1-C_6 alkyl, preferably methyl, or optionally substituted C_3-C_7cycloalkyl, preferably cyclopropyl, or optionally substituted C_0-C_6alkylaryl, preferably optionally substituted phenyl.

A particularly preferred configuration for A is $COOR^1$, especially where R^1 is C_1-C_6 alkyl, such as methyl, ethyl, or tert-butyl and most preferably hydrogen.

Substituent -W-R8 to the cyclic P2 group can employ any of the proline substituents which are extensively described in WO 00/59929, WO 00/09543, WO 00/09558, WO 99/07734, WO 99/07733, WO 02/60926, WO 03/53349, WO03064416, WO03064455, WO03064456, WO0 03/99274, WO03/99316 and the like,

Preferred W functions include W is -OC(=O)NH-, -OC(=O)-, -NH-, $-NR^{8'}$-, $-NHS(O)_2$- or -NHC(=O)-, especially --OC(=O)NH- or --NH-. Favoured R^8 groups for such W functions include optionally substituted C_0-C_3-alkylcarbocyclyl or C_0-C_3-alkylheterocyclyl, including those described in WO0009543, WO0009558 and WO 00/174768. For example ester substituents include those disclosed in WO 01/74768 such as C_1-C_6 alkyl, C_0-C_3aryloyl, particularly (optionally substituted) benzoyl or C_0-C_3 het-oyl, especially



This publication also describes alternative –W-R^8 possibiliteis such as C_1-C_6 alkyl, such as ethyl, isopropyl, C_0-C_3-cycloalkyl such as cyclohexyl, 2,2-difluoroethyl, -C(=O)NRc, where Rc is C_1-C_6 alkyl, C_0-C_3-cyclopropyl, C_0-C_3-aryl or C_0-C_3-heterocyclyl.

Currently preferred W functions include –S- and especially –O-. Convenient values for R^8 in such embodiments include C_0-C_3alkylaryl, or C_0-C_3alkylhetroaryl either of which is optionally mono, di, or tri substituted with R^9, wherein;

R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, NO_2, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C_1-C_6alkyl, C_0-C_3alkylaryl, C_0-C_3alkylhetroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, C_1-C_3 alkyl amide), sulfonylC_1-C_3alkyl, NO_2, OH, halo, trifluoromethyl, carboxyl, or hetroaryl.

Preferred R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, amino, di-(C_1-C_3 alkyl)amino, C_1-C_3alkylamide, aryl or hetroaryl, the aryl or hetroaryl being optionally substituted with R^{10}; wherein

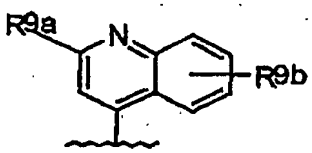
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino, mono- or di-C_1-C_3 alkylamino, amido, C_1-C_3 alkylamide, halo, trifluoromethyl, or hetroaryl.

Preferred R^{10} include C_1-C_6alkyl, C_1-C_6alkoxy, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3-alkylamide, halo, or hetroaryl.

Particularly preferred R^{10} include methyl, ethyl, isopropyl , tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3alkylamide, or C_1-C_3alkyl thiazole.

Especially preferred R^8 include 1-naphthlmethyl, 2-naphtylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl unsubstituted , mono, or disubstituted with R^9 as defined, in particular 1-naphthylmethyl, or quinolinyl unsubstituted , mono, or disubstituted with R^9 as defined.

A currently preferred R^8 is:

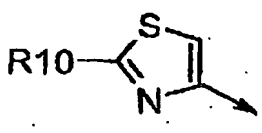


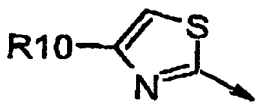
wherein R^{9a} is C_1-C_6 alkyl; C_1-C_6alkoxy; thioC_1-C_3alkyl; amino optionally substituted with C_1-C_6alkyl; C_0-C_3alkylaryl; or C_0-C_3 alkylheteroaryl, C_0-C_3 alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with R^{10} wherein

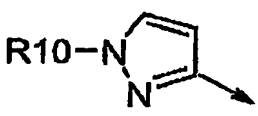
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, C_1-C_3alkyl amide, heteroaryl or heterocyclyl; and

R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3alkyl)amino, (C_1-C_3alkyl) amide, NO_2, OH, halo, trifluoromethyl, carboxyl.

Conveninet R^{9a} include aryl or heteroaryl, all optionally substituted with R^{10} as defined, especially where R^{9a} is selected from the group consisted of :

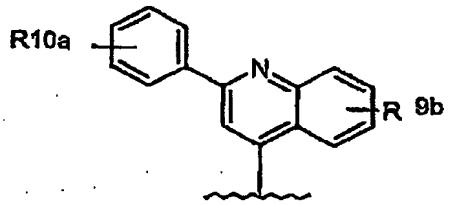






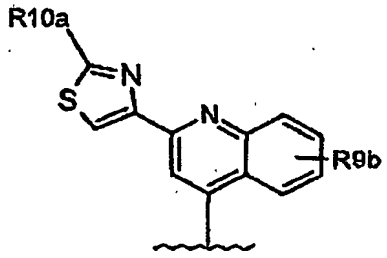
wherein R^{10} is H, C_1-C_6alkyl, or C_0-C_3alkyl-C_3-C_6cycloalkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3alkyl)amide, heteroaryl or heterocyclyl.

R^{9a} is conveniently phenyl and thus R^8 is:



wherein R^{10a} is H, C_1-C_6alkyl; C_1-C_6alkoxy; or halo; and R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3alkyl)amino, (C_1-C_3alkyl)amide, NO_2, OH, halo, trifluoromethyl, carboxyl.

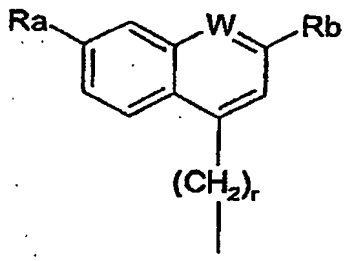
An alternative preferred R^8 is:



wherein R^{10a} is H, C_1-C_6alkyl, or C_0-C_3alkyl-C_3-C_6cycloalkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3 alkyl)amide, heteroaryl or heterocyclyl; and R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3 alkyl)amino, (C_1-C_3 alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl.

In the immediately above described embodimetns R^{9b} is conveniently C_1-C_6-alkoxy, preferably methoxy.

A further ether substituent R^8 has the formula

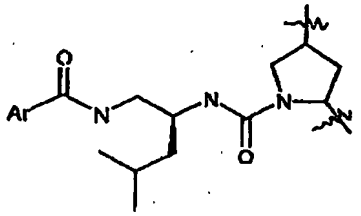


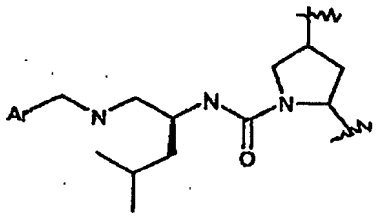
where W is N or CH, r is 0 or 1, Ra is H, C_1-C_6 alkyl, C_0-C_3cycloalkyl, C_1-C_6 alkyloxy, hydroxy or amine and Rb is H, halo, C_1-C_6 alkyl, C_0-C_3cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 thioalkyl, cycloalkylC_0-C_3alkyloxy, C_1-C_3alkyloxyC_1-C_3alkyl, C_0-C_3aryl or C_0-C_3heterocyclyl. A particularly preferred ether substituent is 7-methoxy-2-phenyl-quinolin-4-yl oxy.

Preferred P3 groups include aliphatic amino acids, such as L-valyl, L-leucyl, L-isoleucyl or L- t-leucyl. Further preferred P3 groups, as shown in WO 02/01898 include C_0-C_3 cycloalkyl, especially cyclohexylalanine, optionally substituted with CO_2Rg, where Rg is H, is C_1-C6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl or amine; or N-acetylpiperidine or tetrahydropyran. Preferred R^{11} groups thus include C_1-C_6alkyl, C_0-C_3 alkylC_3-C_7 cycloalkylyl, C_0-C_3alkylaryl or C_0-C_3 alkylheteroaryl, any of which is optionally substituted with hydroxy, halo, amino, C_1-C_6alkoxy, C_1-C_6thioalkyl, $COOR^{14}$, carboxyl, (C_1-C_6alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl, especially where the substituent is hydroxy or $COOR^{14}$.

Particularly preferred R^{11} include tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimethyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl. The most preferred R^{11} values are currently tert-butyl, iso-butyl, or cyclohexyl.

Representative embodiments of P3 groups which lack a carboxy function (ie variable T is absent) include:





where Ar is carbocyclyl or heterocyclyl, and the corresponding variants of formula VI.

R^{15} is preferably optionally substituted C_1-C_6alkyl, C_3-C_7cycloalkyl or C_0-C_3alkylC_3-C_7cycloalkyl. Preferred P4 groups are typically aliphatic amino acids such as L-valyl, L-leucyl, L-isoleucyl , L-t-leucyl or L-cyclohexylalanine and thus favoured R^{15} groups include cyclohexyl, cyclohexylmethyl, tert-butyl, iso-propyl, or iso-butyl.

Preferred G values include –NRy-, especially wherein Ry is methyl or preferably H, or hydrazine.

A further preferred G value is O thereby defining an ester with the carbonyl of P4 (if present) or the carbonyl of P3 (if present) or an ether in the case of variants wherein group U is absent. Conventional pharmaceutically acceptable ethers or esters capping groups for R^{16} include C_1-C_6alkyl (especially methyl or t-butyl), C_0-C_3alkylheterocyclyl (especially pyridyl, benzimidazolyl, piperidyl, morpholinyl, piperazinyl) or C_0-C_3alkylcarbocyclyl (especially phenyl, benzyl, indanyl) any of which is optionally substituted with hydroxy, halo, amino, or C_1-C_6alkoxy.

Favoured R^{16} groups thus include 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, phenyl, benzyl, 2-pyridylmethyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

Currently preferred R^{16} groups include 2-indanol, indan, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, 2,3-methylenedioxybenzyl, or cyclohexylmethyl.

Unnatural amino acids include L-amino acids wherein the side chain is not one of the 20 naturally occurring amino acids. Examples of non-natural amino acids include L-beta-methylsulfonylmethylalanine, L-cyclohexylalanine, L-tertiary-leucine, L-norleucine, L-norvaline, L-ornithine, L-sarcosine, L-citurline, L-homophenylalanine, L-homoserine, L-beta-(1-napthyl)alanine, L-beta-(2-napthyl)alanine etc. Non natural amino acids also include the D-amino acids corresponding to the 20 natural amino acids and D-amino acids bearing other side chains, such as those listed above.

'C_1-C_6-alkyl' as applied herein is meant to include straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. The alkyl group may have an unsaturated bond. Additionally, any C_1-C_6-alkyl may optionally be substituted by one or two halogens and/or a heteroatom S, O, NH. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or 2 hydrogen atoms.

'C_1-C_3-alkyl' as applied herein includes methyl, ethyl, propyl, isopropyl, cyclopropyl, any of which may be optionally substituted as described in the paragraph above or in the case of C_2 or C_3, bear an unsaturated bond such as CH_2=CH.

'Amine' includes NH_2, NHC_1-C_3-alkyl or N(C_1-C_3-alkyl)$_2$.

'Halo' as applied herein is meant to include F, Cl, Br, I, particularly chloro and preferably fluoro.

"'C_0-C_3-aryl' as applied herein is meant to include a phenyl, naphthyl or phenyl fused to C_3-C_7 cyclopropyl such as indanyl, which aryl is directly bonded (ie C_0) or through an intermediate methyl, ethyl, propyl, or isopropyl group. Unless otherwise indicated the aryl group is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl,

amino, azido, oxo, mercapto, nitro C_0-C_3carbocyclyl, C_0-C_3-heterocyclyl. "Aryl" has the corresponding meaning.

'C_0-C_3-carbocyclyl' as applied herein is meant to include 'C_0-C_3-aryl' and C_3-C_7 cycloalkyl. Unless otherwise indicated the aryl group is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto, nitro C_0-C_3carbocyclyl, C_0-C_3-heterocyclyl. "Carbocyclyl" has the corresponding meaning.

'C_0-C_3-heterocycylyl' as applied herein is meant to include a monocyclic, saturated or unsaturated, heteroatom-containing ring such as piperidinyl, morpholinyl, piperazinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, or any of such groups fused to a phenyl ring, such as quinolinyl, benzimidazolyl etc, which ring is bonded directly e ie (C_0) or through an intermediate methyl, ethyl, propyl, or isopropyl group. Unless otherwise indicated the hetero ring is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto, nitro, C_0-C_3 carbocyclyl, C_0-C_3-heterocyclyl. "Heterocyclyl" and "Heteroaryl" has the corresponding meaning.

Typically heterocycyl and carbocyclyl groups are thus a monocyclic ring with 5 or especially 6 ring atoms, or a bicyclic ring structure comprising a 6 membered ring fused to a 4, 5 or 6 membered ring.

Typical such groups include C_{3-8} cycloalkyl, phenyl, benzyl, tetrahydronaphthyl, indenyl, indanyl, heterocyclyl such as from azepanyl, azocanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl,

benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl and quinoxalinyl, any of which may be substituted as defined herein.

The saturated heterocycle thus includes radicals such as pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidinylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1 -dioxide and imidazolidinyl-2,4-dione, whereas the unsaturated heterocycle include radicals with an aromatic character such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl. In each case the heterocycle may be condensed with a phenyl ring to form a bicyclic ring system.

In general preferred monocyclic rings include substituted pyridyl, substituted pyrimidyl, substituted phenyl, particularly phenyl substituted with a cyclic group such as pyrrolidine-1-yl, piperidine-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl, 2-morpholin-4-yl-ethylamino, and piperazin-1-yl, piperid-4-yl or N-piperazinyl, N-substituted with Ra or piperidin-1-yl which is 4-substituted with -NRaRb.

Synthesis of the compounds of the present invention can be performed by different chemical strategies in solution or solid phase or a combination of both. The suitably protected individual building blocks can first be prepared and subsequently coupled together i.e. P2+P1→ P2-P1. Alternatively, precursors of the building blocks can be coupled together and modified at a later stage of the synthesis of the inhibitor sequence. Further building blocks, precursors of building blocks or prefabricated bigger fragments of the desired structure, can then be coupled to the growing chain,

e.g. R^{16}-G-P3+ E-P2-P1→ R^{16}-G-P3-P2-P1 or R^{16}-G-P4-P3+E-P2-P1→ R^{16}-G-P4-P3-E-P2-P1.

Coupling between two amino acids, an amino acid and a peptide, or two peptide fragments can be carried out using standard coupling procedures such as the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide) method, active ester (pnitrophenyl ester, N-hydroxysuccinic imido ester) method, Woodward reagent K-method, carbonyldiimidazole method, phosphorus reagents or oxidation-reduction methods. Some of these methods (especially the carbodiimide method) can be enhanced by adding 1-hydroxybenzotriazole or 4-DMAP. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

More explicitly, the coupling step involves the dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the present of a coupling agent to form a linking amide bond. Descriptions of such coupling agents are found in general textbooks on peptide chemistry, for example, M. Bodanszky, "Peptide Chemistry", 2nd rev ed., Springer-Verlag, Berlin, Germany, (1993) hereafter simply referred to as Bodanszky, the contents of which are hereby incorporated by reference. Examples of suitable coupling agents are N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N,N'- dicyclohexylcarbodiimide or N-ethyl-N'- [(3dimethylamino) propyl] carbodiimide. A practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy) tris- (dimethylamino) phosphonium hexafluorophosphate, either by itself or in the present of 1-hydroxybenzotriazole or 4-DMAP. Another practical and useful coupling agent is commercially available 2-(lH-benzotriazol-1-yl)-N, N, N',N'- tetramethyluronium tetrafluoroborate. Still another practical and useful coupling agent is commercially available 0-(7-azabenzotrizol-1-yl)-N, N,N', N'-tetramethyluronium hexafluorophosphate.

The coupling reaction is conducted in an inert solvent, e. g. dichloromethane,

acetonitrile or dimethylformamide. An excess of a tertiary amine, e. g. diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine or 4-DMAP is added to maintain the reaction mixture at a pH of about 8. The reaction temperature usually ranges between 0 °C and 50 °C and the reaction time usually ranges between 15 min and 24 h.

The functional groups of the constituent amino acids generally must be protected during the coupling reactions to avoid formation of undesired bonds. The protecting groups that can be used are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), hereafter referred to simply as Greene, the disclosures of which are hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected as an ester that can be cleaved to give the carboxylic acid. Protecting groups that can be used include 1) alkyl esters such as methyl, trimethylsilyl and t.butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved by mild base or mild reductive means such as trichloroethyl and phenacyl esters.

The α-amino group of each amino acid to be coupled must be protected. Any protecting group known in the art can be used. Examples of such groups include: 1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted bensyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate groups such as tertbutyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl groups such as triphenylmethyl and benzyl; 6) trialkylsilyl such as trimethylsilyl; and 7) thiol containing groups such asphenylthiocarbonyl anddithiasuccinoyl. The preferred α-amino protecting group is either Boc or Fmoc. Many amino acid derivatives suitably protected for peptide synthesis are commercially available.

The α-amino protecting group is cleaved prior to the next coupling step. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethylformamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0 °C and room temperature usually 20-22 °C.

Any of the natural or non-natural amino acids having side chain functionalities will typically be protected during the preparation of the peptide using any of the above described groups. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups for these side chain functionalities depend upon the amino acid and presence of other protecting groups in the peptide. In the selection of such protecting groups it is desirable that the group is not removed during the deprotection and coupling of the α-amino group.

For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chain of amino acids such as Lys and Arg; acetamidomethyl, benzyl (Bn), or tert-butylsulfonyl moities can be used to protect the sulfide containing side chain of cysteine; benzyl (Bn) ethers can be used to protect the hydroxy containing side chains of serine, threonine or hydroxyproline; and benzyl esters can be used to protect the carboxy containing side chains of aspartic acid and glutamic acid.

When Fmoc is chosen for the α-amine protection, usually tert. butyl based protecting groups are acceptable. For instance, Boc can be used for lysine and arginine, tert.butyl ether for serine, threonine and hydroxyproline, and tert-butyl ester for

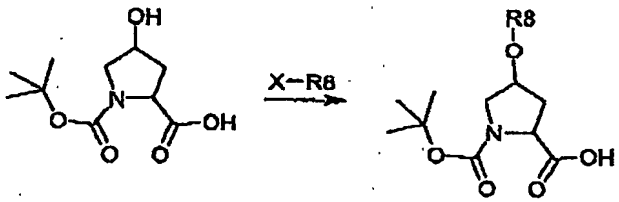
aspartic acid and glutamic acid. Triphenylmethyl (Trityl) moiety can be used to protect the sulfide containing side chain of cysteine.

Once the inhibitor sequence is completed any protecting groups are removed in whatever manner is dictated by the choice of protecting groups. These procedures are well known to those skilled in the art.

In compounds of Formula I, the P2 unit comprises a nitrogen-containing ring residue which is substituted with the W and R8 moieties.

Synthesis of heterocyclic P2 building blocks

Compounds wherein W is O and R8 is alkyl, C_0-C_3 carbocycylyl, C_0-C_3-heterocycylyl can be prepared according to the procedure described by E. M. Smith et al. (J. Med. Chem. (1988), 31, 875-885), as depicted in Scheme 1, which illustrates the technique in a moiety wherein q and k are 1.



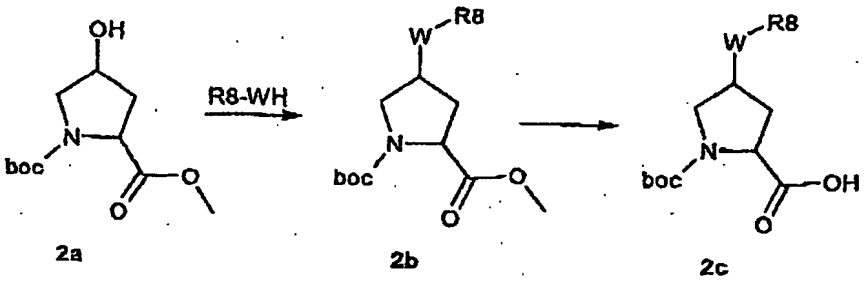
1a 1b

Scheme 1

Commercially available Boc-4-(R)-hydroxyproline, or any suitable hydroxy substituted proline analogue, such as an hydroxypiperidoic acid is treated with a base such as sodium hydride or potassium t.butoxide in a solvent like dimethylformamide and the resulting alkoxide is reacted with an alkylating agent, R^8-X, wherein X is a suitable leaving group such as a halide like chloride, bromide or iodide, providing the desired substituted proline derivative.

Alternatively, when W is O or S and R^8 is carbocyclyl such as phenyl or heterocyclylyl such as heteroaryl, the P2 building blocks can also be prepared via a

Mitsunobu reaction (Mitsunobu, 1981, Synthesis, January, 1-28; Rano et al., Tetrahedron Lett., 1995, 36, 22, 3779-3792; Krchnak et al., Tetrahedron Lett., 1995, 36, 5, 6193-6196; Richter et al., Tetrahedron Lett., 1994, 35, 27, 4705-4706) as shown in Scheme 2, which illustrates the technique in a moiety wherein q and k are 1.

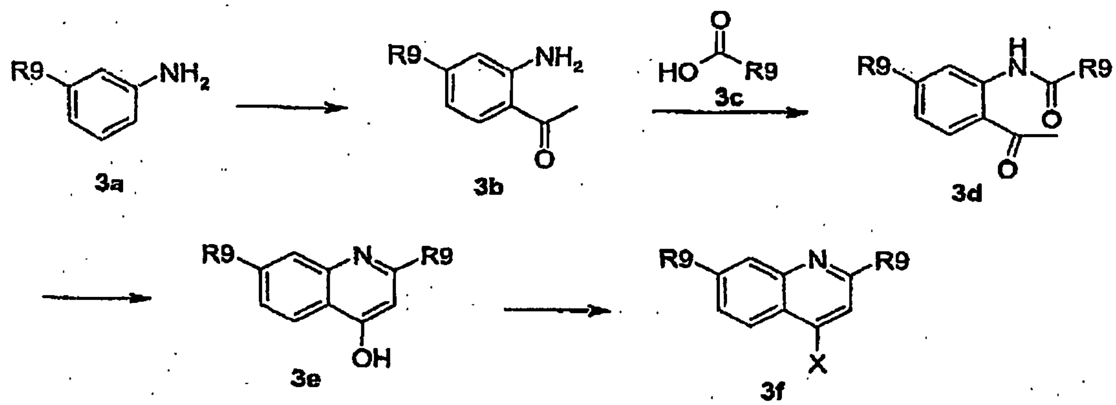


Scheme 2

Treatment of the appropriate hydroxy substituted proline analogue, such as a hydroxypiperidoic acid, here shown as commercially available Boc-4-hydroxyproline methyl ester, with the desired alcohol or thiol (R^8-WH) in the presence of triphenylphosphine and an activating agent like diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) or the like, provides the ester compound (2b). Hydrolysation of the ester to the acid by standard procedures provides the P2 building block (2c).

Alcohol (2a) can alternatively be treated with phosgene thus providing the corresponding chloroformate which upon reaction with an amine, R^8NH_2, in the presence of a base like sodium hydrogen carbonate or triethylamine, provides carbamates i.e. W is -OC(=O)NH-, whereas reaction of alcohol (2a) with an acylating agent, R8-CO-X, like an acid anhydride or acid halide for instance the acid chloride, to provide esters, i.e. W is -OC(=O)-.

Various alcohols R^8-OH, and alkylating agents R^8-X are described in WO 00/09543 and WO00/59929. An example of the synthesis wherein R^8 is a substituted quinoline derivative is shown in Scheme 3.

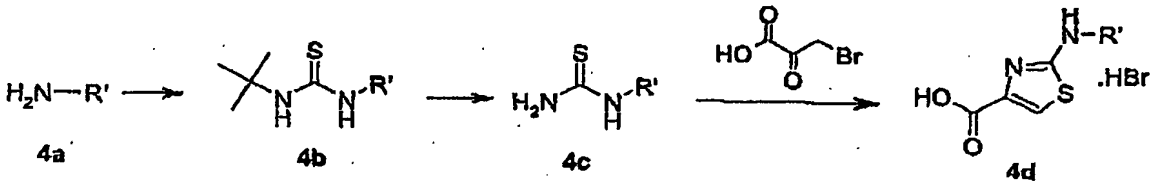


Scheme 3

Friedel-Craft acylation of a suitable substituted aniline (3a), available either commercially or in the literature, using an acylating agent like acetyl chloride or the like in the presence of boron trichloride and aluminium trichloride in a solvent like dichloromethane provides (3b). Coupling of (3b) to a heterocyclic carboxylic acid (3c) under basic conditions, such as in pyridine, in the presence of an activating agent for the carboxylate group, for instance $POCl_3$, followed by ring closure and dehydration under basic conditions like potassium tert.butoxide in tert.butanol provides quinoline derivative (3e). Quinoline derivative (3e) can be coupled in a Mitsunobu reaction to an alcohol as described above, or the hydroxy group can be displaced by a suitable leaving group such as a halide like chloride, bromide or iodide, by treatment of quinoline (3e) with an appropriate halogenating agent for example phosphoryl chloride or the like.

A variety of carboxylic acids with the general structure (3c) can be used in Scheme 3. These acids are available either commercially or in the literature. An example of the preparation of 2-(substituted)-amino-carboxy-aminothiazole derivatives, following the procedure by Berdikhina et al. Chem. Heterocycl. Compd. (Engl. Transl.) (1991),

427-433, is shown below.

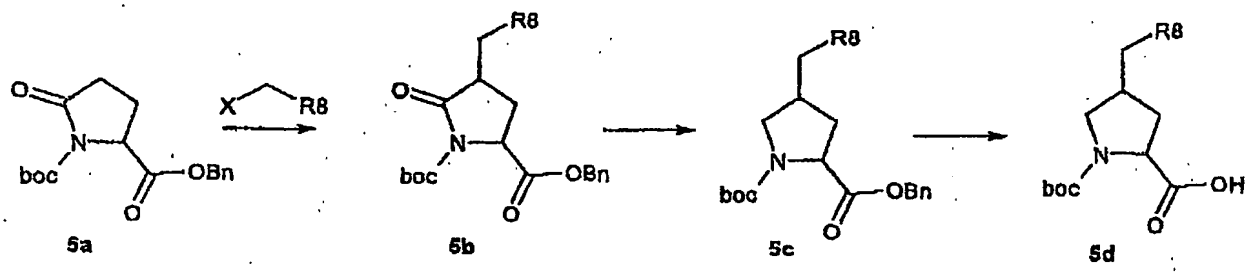


Scheme 4

Thiourea (4c) with different alkyl substituents R' can be formed by reaction of the appropriate amine (4a) with tert.butylisothiocyanate in the presence of a base like diisopropylethylamine in a solvent like dichloromethane followed by removal of the tert. butyl group under acidic conditions. Subsequent condensation of thiourea derivative (4c) with 3-bromopyruvic acid provides the acid (4d).

P2 building blocks wherein the R^8 substituent is attached via a nitrogen atom i.e. W is amine, amide or sulphonamide, can be prepared from aminoproline analogues achieved either from a suitable commercially available aminoproline, etc derivative or by transforming the hydroxy group of the corresponding hydroxy derivative into an azide group for example by transforming the hydroxy group into a suitable leaving group such as a mesylate or halogen like chloride, followed by substitution of the leaving group with azide or by the use of an azide transfer agent like diphenylphosphoryl azide (DPPA). Reduction of the azide by catalytic hydrogenation or any other suitable reduction method provides the amine. The amino derivative can be reacted with an alkylating agent of the general formula R^8-X wherein R^8 and X are as described for scheme 1, to form compounds wherein W is –NH-. Reaction of the aminoproline analogue with an acid of the general formula R^8-COOH under standard amide coupling conditions provides compounds wherein W is -NHC(=O)-, whereas reaction of the aminoproline analogue with an appropriate derivative of sulphonic acid, R^8-$S(O)_2$-X where X is a leaving group for example chloride, in the presence of a base, provides sulphonamides. It will be apparent that corresponding reactions will be available for P2 groups with other ring sizes and substitution pattern.

4-Substituted heterocyclyl derivatives such as 4-substituted proline for use as P2 building blocks where W is $-CH_2-$ can be prepared as shown in Scheme 5, which illustrates the technique on a moiety where q and k is 1, according to the procedures described by J. Ezquerra et al., Tetrahedron, 1993, 38, 8665-8678 and C. Pedregal et al. Tetrahedron Lett., 1994, 35, 2053-2056.



Scheme 5

Treatment of suitably acid protected pyrrolidone or piperidinone such as commercially available Boc-pyroglutamic acid (5a) with a strong base such as lithium diisopropylamide in a solvent like tetrahydrofuran followed by addition of an alkylating agent R^8-CH_2-X where X is a suitable leaving group such as a halide like chloride or bromide, followed by reduction of the amide and deprotection of the ester gives the desired compound (5d).

Compounds with alternative ring size and/or position of the $W-R^8$ substituent of the proline derivatives in scheme 1, 2 and 5 may also be used in the preparation of compounds according to the present invention. For example, alkylation of commercially available 3-hydroxyproline provides compounds of the general formula (I) wherein k is 0 and q is 2. Correspondingly, alkylation of 5-hydroxyproline, prepared for example as described by Hallberg et al., J. Med. Chem. (1999), 4524-4537, provides compounds of the general formula (I) wherein k is 2 and q is 0.

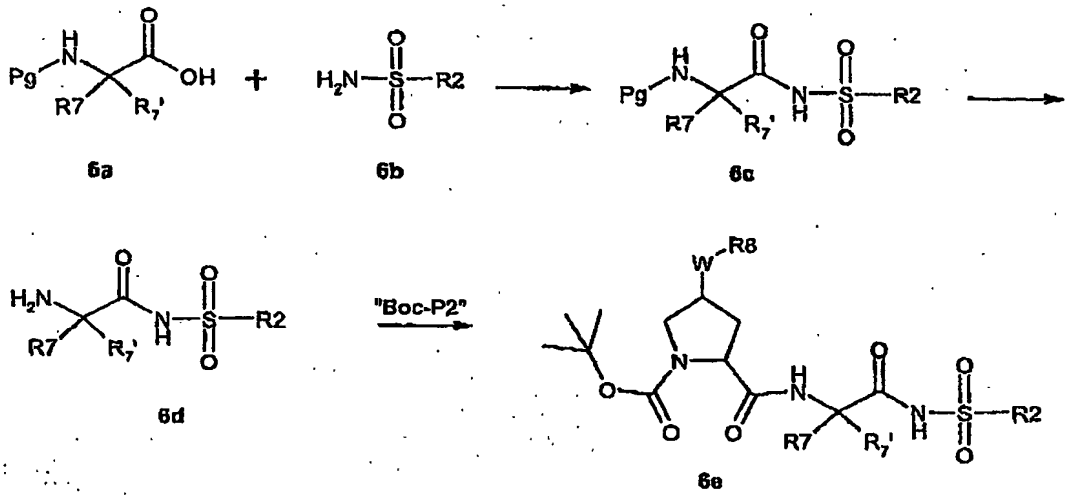
Various methods for the preparation of hydroxylated 2-piperidine carboxylic acids are described in the literature se for instance Celestini et al., Org. Lett., (2002), 1367-1370, Hoarau et al., Tetrahedron: Asymmetry, (1996), 2585-2594, Zhu et al., Tetrahedron Lett., 41, (2000), 7033-7036. For example, the corresponding pyridine carboxylic acids can be reduced to provide hydroxylated 2-piperidine carboxylic acids. Enzymatical methods can also be used for the preparation of hydroxylated proline analogues. For example, a 3-hydroxy substituent can be introduced on commercially available 4, 5, and 6 membered heterocyclic acids by the use of proline 3-hydroxylase as described by Ozaki et al., Tet. Letters, 40, (1999), 5227-5230.

Additional P2 building blocks, especially for compounds of formula VI are described in Schemes 11-15 below.

Synthesis and introduction of P1 building blocks.

The amino acids used in the preparation of P1 fragments are available either commercially or in the literature, see for example WO 00/09543 and WO00/59929 from Boehringer-Ingelheim.

Scheme 6 shows an example of the preparation of a sulphonamide derivative to be used as a P1 fragment, and the subsequent coupling to a Boc protected P2 building block.



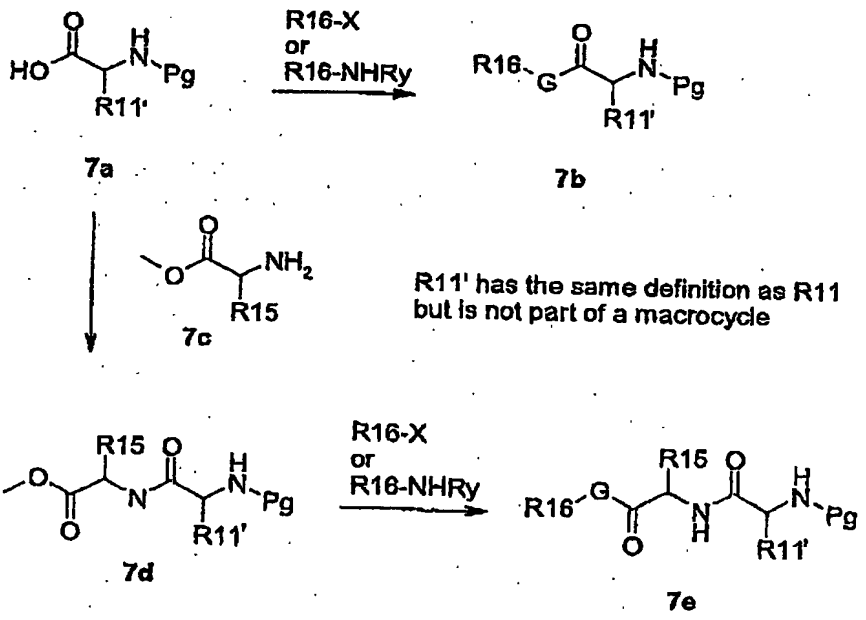
Scheme 6

The sulphonamide group can be introduced on a suitably protected amino acid (6a) by treatment of the amino acid with a coupling agent, for example N,N'-carbonyldiimidazole (CDI) or the like, in a solvent like THF followed by reaction with the desired sulphonamide (6b) in the presence of a strong base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the amino acid can be treated with the desired sulphonamide (6b) in the presence of a base like diisopropyl ethylamine followed by treatment with a coupling agent like PyBOP® to effect the introduction of the sulphonamide group. Removal of the amino protecting group by standard methods and subsequent coupling to a P2 building block, prepared as described above, using standard methods for amide bond formation, like with a coupling agent as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in the presence of a base such as diisopropylamine in a solvent like dimethylformamide, gives Boc protected P2-P1 construct (6e). Alternatively, the sulphonamide group can be introduced at a later stage of the synthesis, for example as the last step. In this case the carboxylic acid is appropriately protected, for example as the methyl ester, and appropriately deprotected prior to the coupling of the sulphonamide group, for example with aqueous lithium hydroxide.

P1 building blocks for the preparation of compounds according to general formula I and VI wherein A is an ester or an amide can be prepared by reacting amino acid (6a) with the appropriate amine or alcohol respectively under standard conditions for amide bond or ester formation. P1 building blocks wherein A is $CR^4R^{4'}$ are described in Oscarsson et al Bioorg Med Chem 2003 11(13) 2955-2963 and PCT/EP03/10595 filed 23.09.2003, the contents of which are incorporated by reference.

Synthesis of capped building blocks

The building blocks R^{16}-G-P3 and R^{16}-G-P4-P3 can be prepared as generally depicted in scheme 7.

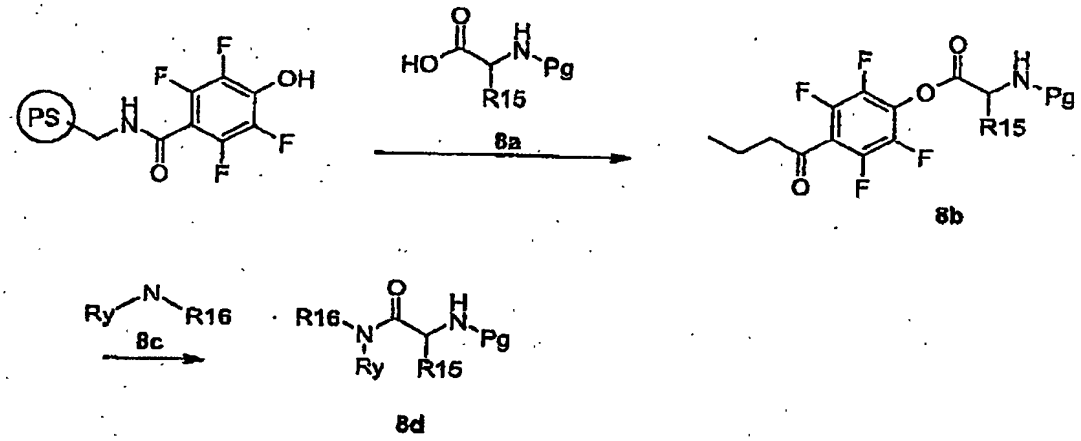


Scheme 7

A suitable N-protected amino acid (7a) can be coupled with an amino capping group (R^{16}-NHRy) using standard peptide coupling conditions like with coupling agents such as HATU, DCC, HOBt or the like in the presence of a base such as DIEA or DMAP in a solvent like dichloromethane, chloroform or dimethylformamide or a mixture thereof and ester formation conditions like providing amides i.e. G is NHRy (7b). Alternatively, reaction of amino acid (7a) with a compound of general formula R^{16}-X where R^{16} is as defined above and X is a leaving group such as a halide, in

the presence of a base like cesium carbonate or silver (I) oxide provides esters, i.e. G is O (7b). On the other hand, amino acid (7a) can be coupled to a second, suitably O-protected, amino acid (7d) using standard peptide coupling conditions as described above, providing (7e). Displacement of the ester group with a suitable capping group (7b) provides fragment (7f) useful for the preparation of compounds according to the present invention wherein m and n are 1.

When G is N-Ry, the capped P3 or P2 building block can also be prepared on solid support as exemplified in Scheme 8.



Scheme 8

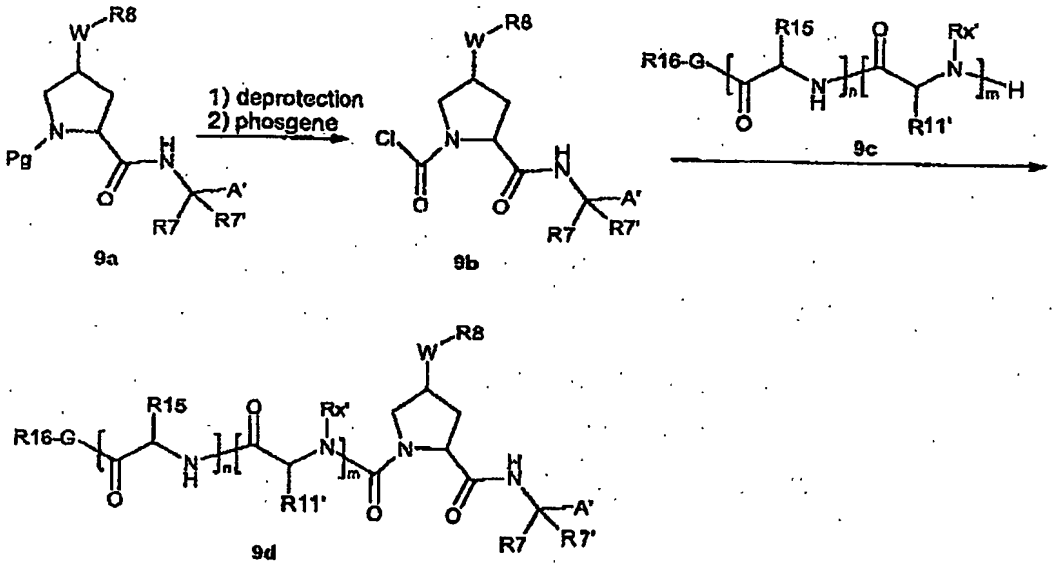
An appropriate N-protected, for example Boc protected, amino acid (8a) can be immobilized on a solid support, here exemplified by Agronaut resin PS-TFP, by reacting the amino acid with the desired solid support in the presence of coupling reagent like N,N'-diisopropylcarbodiimide and a base like DMAP in a solvent like dichloromethane and dimethylformamide. The immobilized amino acid can then be cleaved from the support with a suitable capping group (8c) thus giving fragments useful for the preparation of compounds according to the present invention wherein m or n is 1. Optionally the amino protecting group can be removed followed by coupling of an appropriate amino acid using standard methods thus providing

fragments useful for the preparation of compounds according to the present invention wherein m and n are 1.

Hydrazine containing P3 and P3-P4 building blocks can be prepared by the use of tert. butyl carbazate instead of amino acid 7a and 8a in schemes 7 and 8 respectively thus providing intermediates for the synthesis of compounds wherein T is NRd.

Coupling of a capping group or a capped building block to the P2-P1 construct

The R^{16}-G, R^{16}-G-P3 or R^{16}-G-P4-P3 building block linked via a urea functionality to the P2-P1 construct, can be introduced as depicted in scheme 8, which illustrates the technique with a variant in which P2 is a heterocyclic residue.



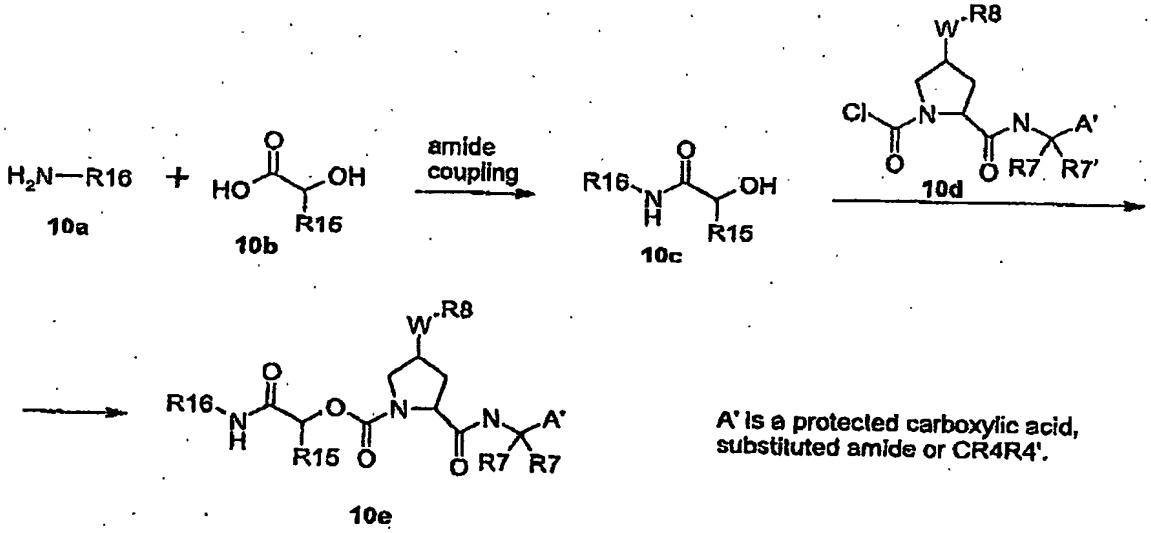
Rx' and R11' have the same definitions as Rx and R11 respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or CR4R4'.

Scheme 9

A chlorocarbamate group can be formed onto the ring amine of the P2-P1 construct (9a) by removal of the amine protection group by standard procedures, like acidic treatment with for example TFA in dichloromethane or the like when the Boc group is used, followed by reaction of the free amine with phosgene in toluene in the

presence of a base such as sodium hydrogen carbonate or triethylamine in a solvent like tetrahydrofuran. Subsequent reaction of the formed electrophilic center with the amino group of a R^{16}-G, R^{16}-G-P3 or R^{16}-G-P4-P3 building block (9c) in a solvent like dichloromethane in the presence of a base like sodium hydrogen carbonate provides (9d). Compounds of general formula (I) wherein E is C=S, S(=O) or $S(=O)_2$ can be prepared according to the above procedure but with the use of reagents like thiocarbonyl diimidazole, thionyl chloride or sulphuryl chloride respectively instead of phosgene.

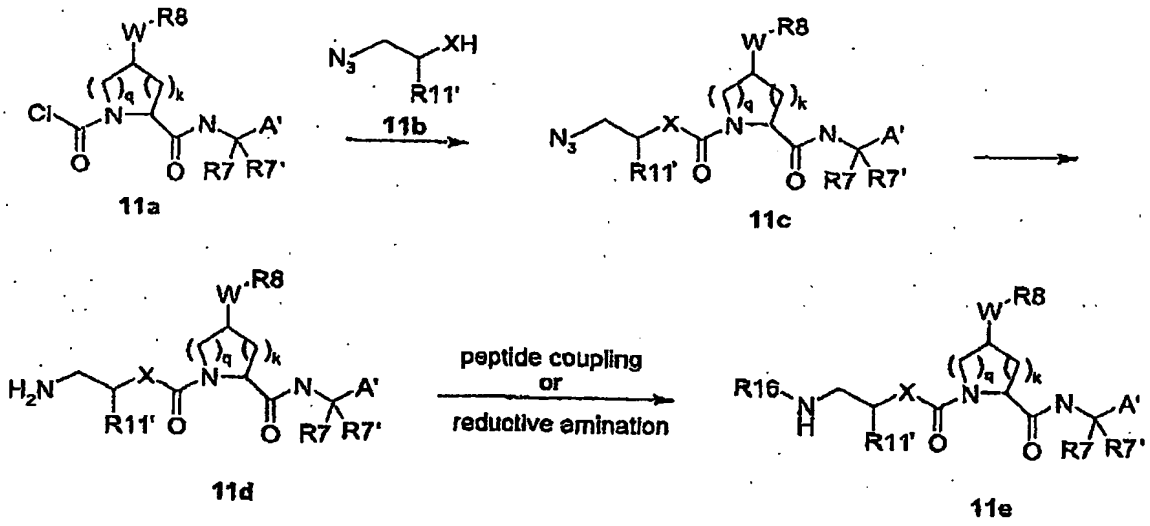
The linkage between the P2 and P3 building blocks can also be via a carbamate group and a general route to such compounds is depicted in Scheme 10, which illustrates the technique with a variant in which P2 is a proline derivative.



Scheme 10

The desired, optionally protected, amino capping group (10a) is coupled to a hydroxy acid (10b) using standard peptide coupling techniques followed by reaction with the electrophilic P2 building block (10d) described above and optional deprotection provides construct (10e).

Compounds lacking a carboxy group in the P3 unit can be prepared as illustrated in Scheme 11, which illustrates the technique as applied to a compound of Formula I



R11' has the same definition as R11but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or CR4R4'.

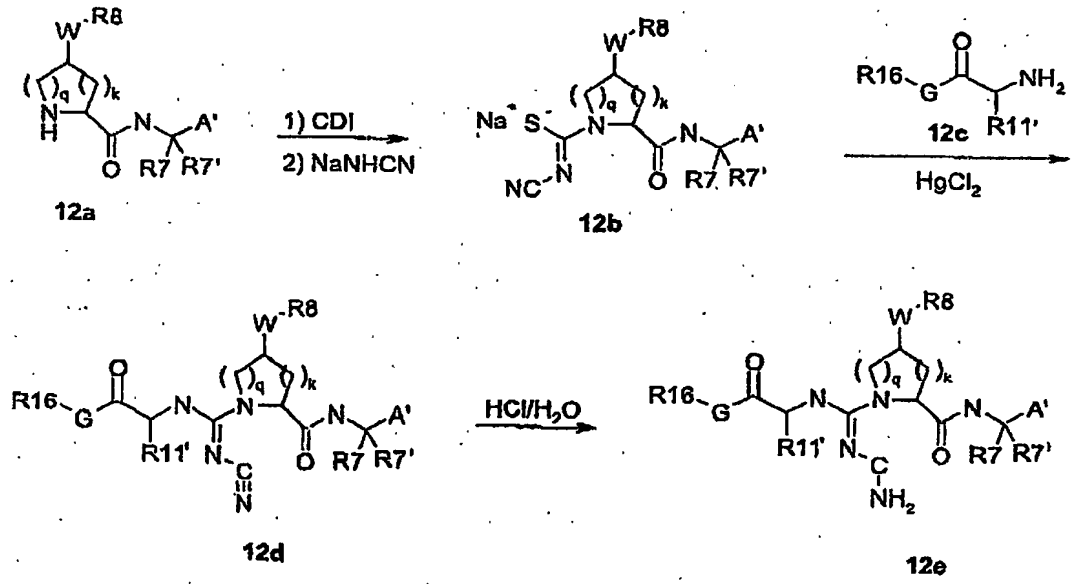
Scheme 11

Chlorocarbamoyl derivative (11a) can be reacted in a displacement reaction with an azide derivative (11b), prepared by methods known from the literature, in the presence of a base like sodium hydrogen carbonate to give (11c). X is as described for general formula (I). Reduction of the azide function for example by polymer bound triphenyl phosphine in a solvent like methanol or any other suitable reduction method provides intermediate (11d) which subsequently can be reacted with an acid under peptide coupling conditions or with an amine in a reductive amination reaction providing amides and secondary amines respectively.

Instead of using the azide derivative (11b) in the displacement reaction with chlorocarbamate (11a) the corresponding hydroxy derivative can be used. Subsequent reaction of the formed alcohol with a suitable acylating or alkylating agent using the appropriate conditions provides the ester and ether compounds respectively, i.e. G is O in general formula (I).

Although Figure 11 has been described with reference to a compound of Figure I, it will be readily apparent that corresponding methodology is applicable for compounds of the Formula VI.

Alternatively the linkage between the P2 and P3 building blocks can be via a guanidine group and a general route to such compounds is depicted in Scheme 12.



R11' has the same definition as R11but is not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or CR4R4'.

Scheme 12

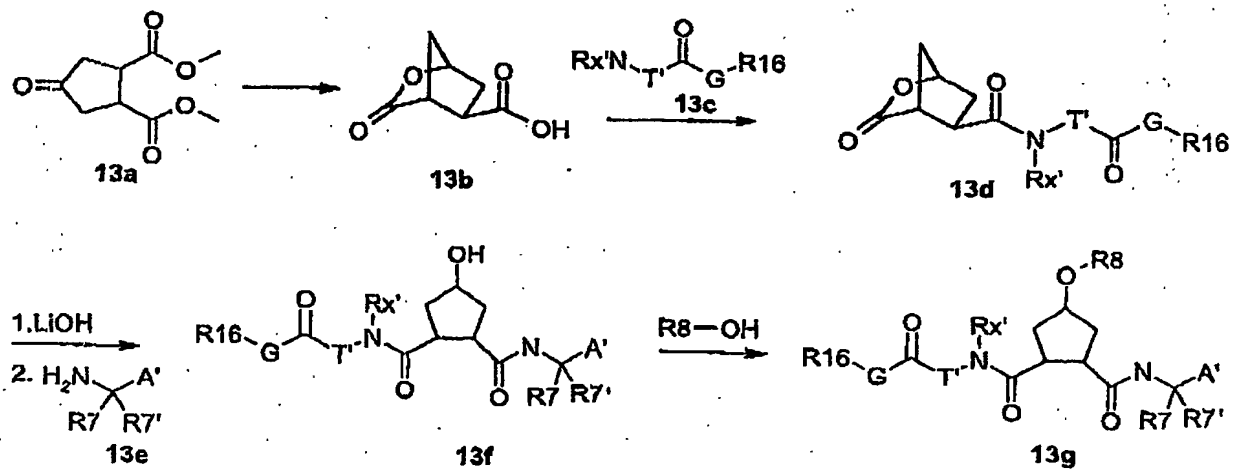
Treatment of the P2-building block (12a) with thiocarbonyl diimidazole or the like in a solvent like dimethylformamide followed by condensation with sodium cyanamide in a solvent like ethanol affords the thiolate intermediate (12b). Reaction of intermediate (12b) with the desired building block, here shown as a capped P3 building block (12c) provides the cyanoguanidine derivative (12d). Other building blocks, R^{16}-G or R^{16}-G-P4-P3, can alernatively be coupled to the intermediate (12b).

Hydrolysis of the cyano group by treatment of (12d) with diluted hydrochloric acid gives the guanylurea derivative (12e).

When R7, R7' and A' contains functional groups, these are suitably protected by methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

Carbocyclic P2 building blocks

A typical route to saturated, carbocyclic P2 bluidling blocks towards compounds of formula VI is shown in Scheme 13, which illustrates the technique with a variant wherein q' is 0 and k is 1.



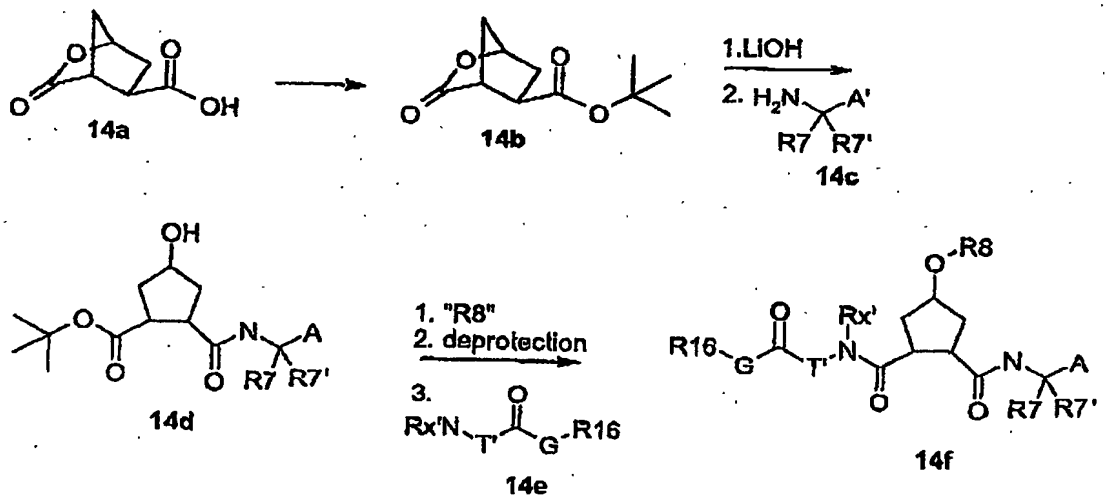
Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or CR4R4'.

Scheme 13

The saturated cycloalkyl scaffold (13b) can be prepared, for example, from 3,4-bis(methoxycarbonyl)cyclopentanone (13a), described by Rosenquist et al. in Acta Chem. Scand. 46 (1992) 1127-1129 by reduction of the keto group with a reduction agent like sodium borohydride in a solvent like methanol followed by hydrolysis of the esters and finally ring closure in acetic anhydride in the presence of pyridine. The

provided bicyclic acid (13b) can then be coupled to the amine function of the desired P3 fragment (13c), P3-P4 fragment or capping group R^{16}-NHRy, using conventional peptide coupling conditions like with HATU and diisopropyl amine in a solvent like dimethyl formamide, giving (13d). Lactone opening of (13d) with for example lithium hydroxide provides the acid which subsequently can be coupled to the amino group of a P1 building block or a precursor of a desired P1 fragment (13e), using conventional peptide coupling conditions. The R^8-substituent of the carbocycel can be introduced for example by a Mitsunobu reaction with the appropriate alcohol as described above or by any other suitable method previously described. When R^7, $R^{7'}$ and A' contains functional groups, these are optionally suitably protected by methods recognized by persons skilled in the art, se for example Bodanzky or Greene cited above.

Scheme 14 shows an alternative route towards saturated compounds of formula VI where the building blocks are introduced in the reversed order, i.e. the P1 fragment is introduced before the capping group, P3 or P3-P4 building block.



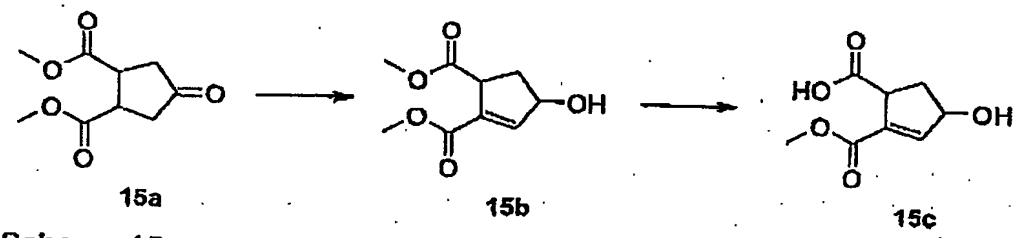
Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle. A' is a protected carboxylic acid, substituted amide or CR4R4'.

Scheme 14

Protection of the acid group of (14a) for example as the tert. butyl ester by treatment with di-tert. butyl dicarbonate in the presence of a base like dimethylaminopyridine and triethylamine in a solvent like dichloromethane provides ester (14b). Lactone opening and coupling of a P1 building block (14c) as described in scheme 13 or directly by the amine group of the P1 fragment provides (14d). Introduction of R^8-substituent as described above followed by removal of the acid protection group by subjecting the ester to acidic conditions like trifluoroacetic acid and triethylsilane in a solvent like methylene chloride and finally coupling of the P3 building block (14e), P3-P4 building block or capping group R^{16}-NHRy, as described above provides (f). When R^7, $R^{7'}$ and A' contain functional groups, these are optionally suitably protected by methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

An unsaturated P2 building block towards the preparation of compounds of formula VI can be prepared as illustrated with cyclopentene below.

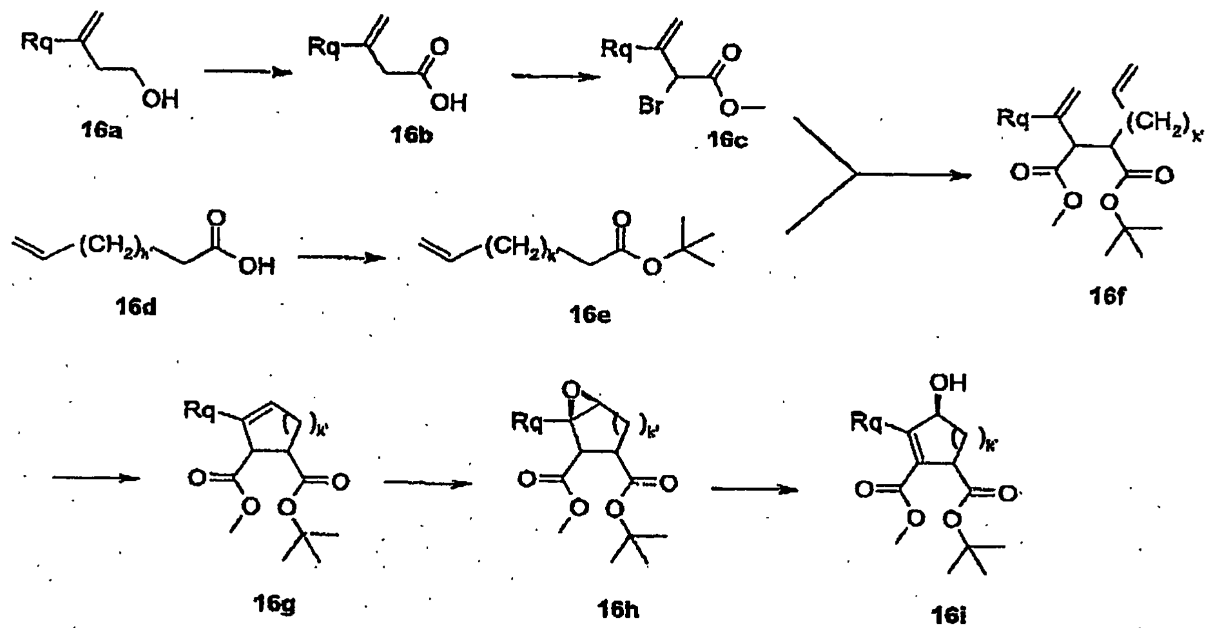
The cyclopentene scaffold is typically prepared as described in scheme 15.



Scheme 15

A bromination-elemination reaction of 3,4-bis(methoxycarbonyl)cyclopentanone (15a) as described by Dolby et al. in J. Org. Chem. 36 (1971) 1277-1285 followed by reduction of the keto functionality with a reduction agent like sodium borohydride provides the unsaturated hydroxy compound (15b). Selective ester hydrolysis using for example lithium hydroxide in a solvent like a mixture of dioxane and water provides hydroxy substituted cyclopentene derivative (15c).

A P2 building block wherein Rq is other than hydrogen, such as a methylated cyclopentene scaffold can be prepared as shown in scheme 16.

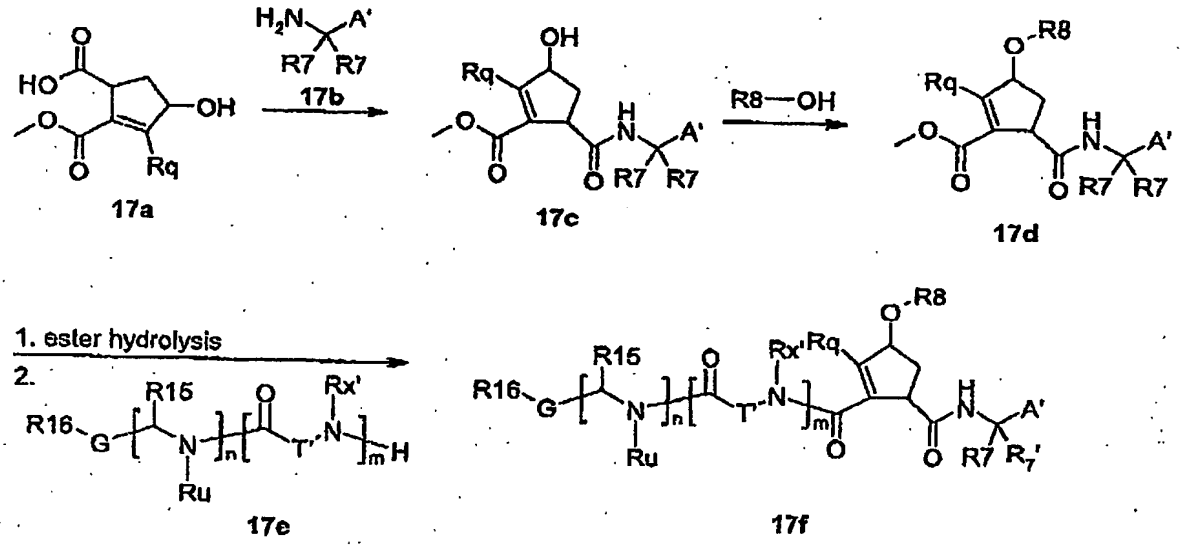


Scheme 16

Oxidation of commercially available 3-methyl-3-buten-1-ol (16a) by the use of an oxidation agent like pyridinium chlorochromate followed by treatment with acetyl chloride, bromine and methanol provides the α-bromo ester (16c). The afforded ester (16c) can then be reacted with the enolate (16e), achieved for example by treatment of the corresponding tert.butyl ester with a base such as lithium diisopropyl amide in a solvent like tetrahydrofuran, to give the alkylated compound (16f). The tert-butyl ester (16e) can be prepared by treatment of the corresponding commercially available acid (16d) where k' is 1 to 3 with di-tert.butyl dicarbonate in the presence of a base like dimethylaminopyridine. Cyclisation of (16f) by an olefin metathesis reaction performed as described above provides cyclopentene derivative (16g). Stereoselective epoxidation of (16g) can be carried out using the Jacobsen asymmetric epoxidation method to furnish the epoxide (16h). Finally, addition of a base like DBN (1,5-diazabicyclo-[4.3.0]non-5-ene) yields the alcohol (16i). Optionally the double bond of compound (16i) can be reduced for example by catalytic

hydrogenation using a catalyst like palladium on carbon which provides the corresponding saturated compound.

The afforded cyclic scaffolds can then be used, as described above, to complete the inhibitor sequence. An example is shown in scheme 17.



Rx' and T' have the same definitions as Rx and T respectively but are not part of a macrocycle.
A' is a protected carboxylic acid, substituted amide or CR4R4'.

Scheme 17

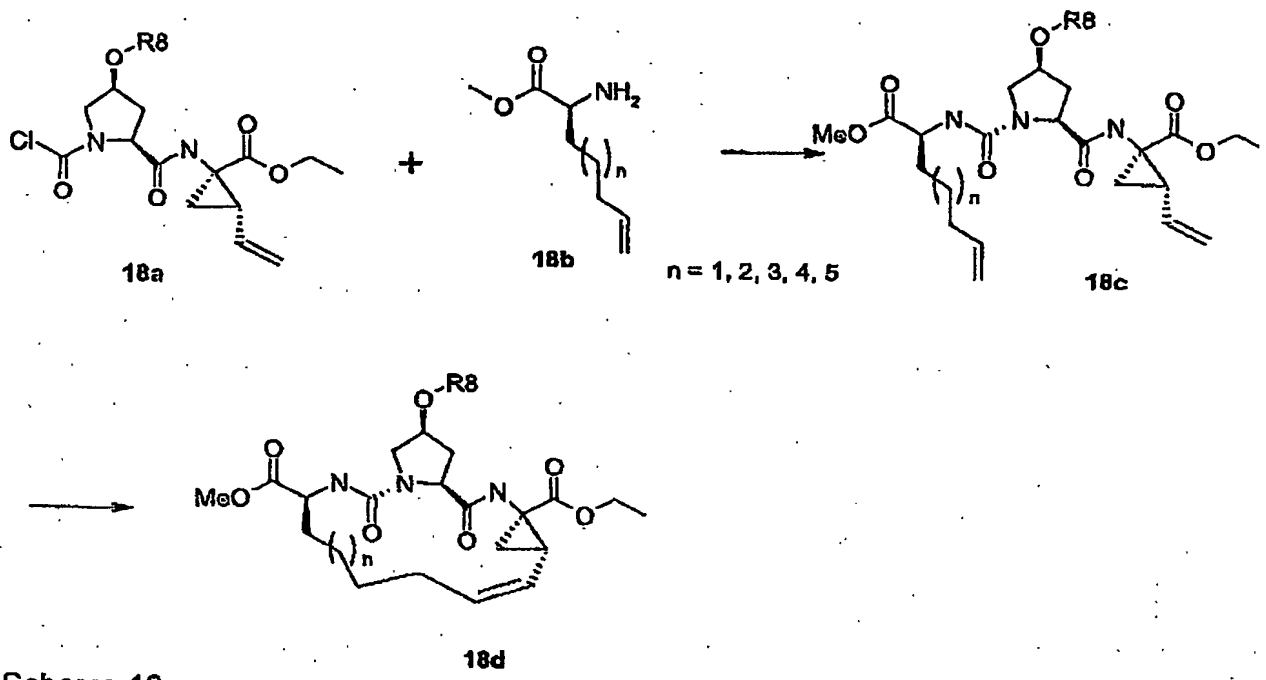
The amino group of a P1-building block or a suitable precursor thereof (17b) can be coupled to the acid of the cyclopentene derivative (17a) using standard amide coupling conditions followed by introduction of the R^8-substituent for example by Mitsunobu conditions as described above to provide (17d). Hydrolysis of the remaining ester and subsequent amide coupling of a desired P3 or P3-P4 building block (17e) optionally followed by manipulations of the P1 part provides cyclopentene containing compounds (17f) according to general formula VI. When R^7, $R^{7'}$ and A' contain functional groups, these are optionally suitably protected by

methods recognized by persons skilled in the art, see for example Bodanzky or Greene cited above.

Formation of macrocyclic compounds

Compounds according to the present invention wherein an alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rx, Rd or R^{11} thus forming a macrocycle, can be prepared as described below. Suitable P1, P2 and P3 building blocks, or precursors thereof, are coupled together using the strategies described above, followed by a ring-closing reaction (macrocyclization). The substituent W-R^8 of the P2 building block can be incorporated via a Mitsunobu reaction as described above, before or after formation of the macrocycle or the assembly can be done with the required substituted proline analogue or carbocycel. For macrocyclic structures extending from the $R^7/R^{7'}$ cycloalkyl to R^{11}, P3 amino acids containing the appropriate side chain can be prepared as described in WO00/59929.

A typical route to macrocyclic compounds is shown in Scheme 18 which illustrates the technique applied to a compound having a heterocyclic P2 and a spiro-cyclopropyl P1, where the macrocycle incorporates the P3 side chain.



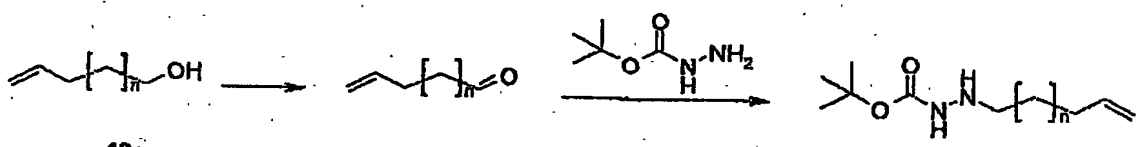
18a 18b 18c 18d

Scheme 18

Coupling of proline derivative (18a) with the appropriate, acid protected, amino acid (18b) using the conditions described above provides (18c). Formation of the macrocycle can then be carried out via an olefin metathesis reaction using a Ru-based catalyst such as the one reported by Miller, S.J., Blackwell, H.E.; Grubbs, R.H. J. Am. Chem. Soc. 118, (1996), 9606-9614, Kingsbury, J. S., Harrity, J. P. A., Bonitatebus, P. J., Hoveyda, A. H., J. Am. Chem. Soc. 121, (1999), 791-799 and Huang et al., J. Am. Chem. Soc. 121, (1999), 2674-2678. It will also be recognized that catalysts containing other transition metals such as Mo can be used for this reaction. Optionally the double bond is reduced and/or the ethyl ester is hydrolysed by standard hydrogenation and/or hydrolysation methods respectively well known in the art. Alternatively the methyl ester can be selectively hydrolysed followed by coupling of a R^{16}-G-P4 building block by standard peptide coupling conditions. The procedure described in Scheme 18 can also be applied to the corresponding carbocyclic analogues described above. When the linker contains a nitrogen atom

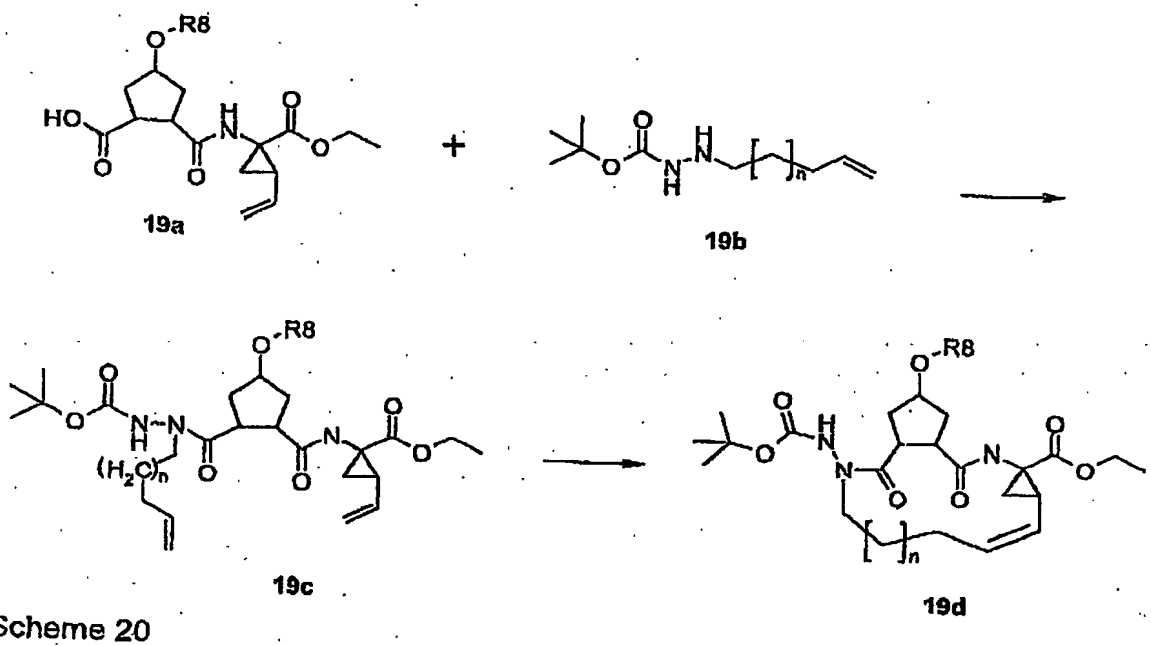
the ring closure can be carried out by reductive amination as described in WO0059929.

Hydrazine containing macrocyclic structures can be prepared by the use of a carbazate derivative, N-alkylated with the appropriate chain, as the P3 unit. Carbazate derivatives can be prepared as described in Scheme 19



Scheme 19

Oxidation of the appropriate alcohol (19a) with a suitable oxidation method like for example with N-methyl morpholine oxide and tetrapropylammonium perruthenate in a solvent like dichloromethane provides ketone (19b). Reductive alkylation of tert.butyl carbazate with the afforded ketone gives the P3 building block (19c). This P3 building block can subsequently be coupled to any of the described P2-P1 building blocks. Scheme 20 exemplifies the coupling of a hydrazine containing P3 building block to a cyclopentane scaffold followed by macrocyclisation.



Scheme 20

Coupling of the carbazate derivative (20b) with a P2-P1 building block (20a) using standard peptide coupling conditions provides intermediate (20c). Ring closure of (20c) by an olefin metathesis reaction as described above gives the macrocyclic compound (20d).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981), which is hereby incorporated by reference. N-protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoracetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl, and the like, carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl,

2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butoxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like; alkyl gropus such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Favoured N-protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butoxycarbonyl (BOC) and benzyloxycarbonyl (Cbz).

Hydroxy protecting group as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)). Hydroxy protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl and other lower alkyl ethers, such as isopropyl, ethyl and especially methyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

In treating conditions caused by flavivirus such as HCV, the compounds of formula I or VI are typically administered in an amount to achieve a plasma level of around 100 to 5000 nM, such as 300 to 2000 nM. This corresponds to a dosage rate, depending on the bioavailability of the formulation, of the order 0.01 to 10 mg/kg/day, preferably 0.1 to 2 mg/kg/day. A typical dosage rate for a normal adult will be around

0.05 to 5 g per day, preferably 0.1 to 2 g such as 500-750 mg, in one to four dosage units per day. As with all pharmaceuticals, dosage rates will vary with the size and metabolic condition of the patient as well as the severity of the infection and may need to be adjusted for concomitant medications.

As is good prescribing practice with antiviral therapy, the compounds of formula I are typically coadministered with other HCV therapies to avoid the generation of drug escape mutants. Examples of such additional HCV antiviral therapies include ribavirin, interferons, including pegylated interferons. Additionally a number of nucleoside analogues and protease inhibitors are in the development and will be amenable to co-administration with the compounds of the invention.

While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers or excipients and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising

bringing a compound of Formula I or VI or its pharmaceutically acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral. Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, stearic acid, glycerol stearate, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid

diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

The compounds of formula I or VI can form salts which form an additional aspect of the invention. Appropriate pharmaceutically acceptable salts of the compounds of formula I include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, isethionate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-napthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids.

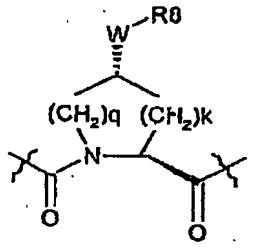
Prodrugs of the compounds of formula I are those compounds which following administration to a patient release a compound of the formula I in vivo generally following hydrolysis in the gut, liver or plasma. Typical prodrugs are pharmaceutically acceptable ethers and especially esters (including phosphate esters) of hydroxy functions, pharmaceutically acceptable amides or carbamates of amine functions or pharmaceutically acceptable esters of carboxy functions. PreferredPharmaceutically acceptable esters include alkyl esters, including acetyl, ethanoyl, butyryl, t-butyryl, stearyl and pivaloyl, phosphate esters and sulphonic esters (ie those derived from

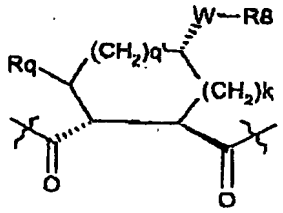
RSO_2OH, where R is lower alkyl or aryl). Pharmaceutically acceptable esters include lower alkyl ethers and the ethers disclosed in WO00/47561, especially methoxyaminoacyl and ethoxyaminoacyl.

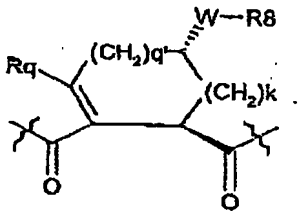
The compounds of the invention have various steric centres and the invention extends to racemates and enantiomers at each of these steric centres.

Typically, the stereochemistry of the groups corresponding to the P3 and P4 side chains (ie R^{15} and/or R^{11}) will correspond to an L-amino acid configuration, although the invention also extends to D-isomers at one or both of these centres.

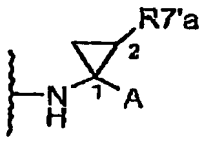
The stereochemistry of the backbone component of the cyclic P2 group (i.e. spanning the carbonyl of the P1 amide bond and the carbonyl or E extending of P3 will typically correspond to L-proline. The stereochemistry of the P2 ring atom to which W is bonded is typically as shown:



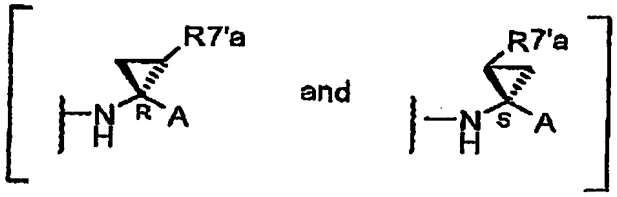




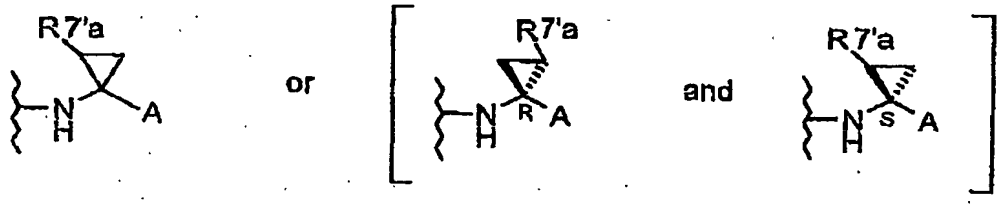
In compounds of the invention wherein R7 and R7' together define a spiroalkyl group, such a spiro-cycloalkyl will typically comprise an $R^{7'a}$ substituent on the spiro-cyclopropyl ring which is is orientated syn to A:



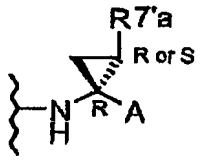
or



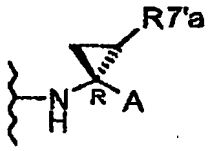
or anti to A:



Conveniently, the spiro carbon of such a spiro-cyclopropyl ring has the R configuration:



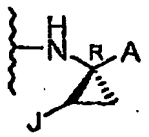
Conveniently an $R^{7'a}$ substituent on a spiro-cyclopropyl ring adjacent to A is in a syn orientation in the following absolute configuration:



Particularly preferred variants have $R^{7'a}$ include ethyl, hence the asymmetric carbon atoms at position 1 and 2 have the R, R configuration.

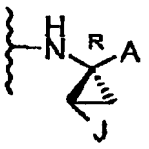
Alternative preferred $R^{7'a}$ include vinyl, hence the asymmetric carbon atoms at position 1 and 2 have the R, S configuration.

Where the compound of the invention is a macrocycle comprising a J group, J is preferably a diastereomer represented by partial structures (i) or (ii):



J syn to the amide (i)

or



J syn to A (ii)

especially where J is syn to A.

Detailed description of the embodiments

Various embodiments of the invention will now be described by way of illustration only with reference to the following non-limiting examples.

Example 1

7-Methoxy-2-phenyl-quinolin-4-ol (1).

To a stirred round bottled flask with toluene (100 mL) ethyl benzoyl acetate (18.7 g, 97 mmol) and *m*-anisidine (12 g, 97 mmol) was added. 4 M HCl in dioxane (0.5 mL) was added and the reaction mixture was refluxed for 6 h (140 °C). The mixture was co-evaporated with toluene. To the crude mixture diphenyl ether (50 mL) was added and the mixture was heated to 280 °C for 2 h. When the theoretical amount ethanol (6 mL) was collected in a Dean Stark trap the heating was stopped and the mixture was cooled to rt. The crude mixture was dissolved in CH_2Cl_2 (100 mL) and stirred for 30 min. The formed precipitate was filtered off and dried which gave 1 (4.12 g, 16.4 mmol, 17 %): pale yellow powder.

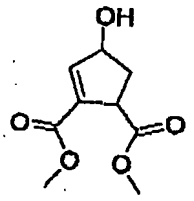
^1H (300 MHz, DMSO-D_6): δ 3.8 (s, 3H), 6.24 (s, 1H), 6.88-6.96 (dd, 1H, J = 9.07 Hz, J = 2.47 Hz), 7.19 (d, 1H, J=2.19 Hz), 7.56 (t, 3H, J = 2.19 Hz), 7.8 (dd, 2H, J = 7.14 Hz, J = 2.19 Hz), 8.0 (d, 1H, J = 9.06 Hz); ^{13}C (75.5 MHz, DMSO-D_6): δ 55.3, 99.6, 106.9, 113.1, 119.1, 126.4, 127.5, 128.8, 130.2, 134.1, 142.2, 149.4, 161.8, 176.4.

Example 2

(Rac)-4-oxocyclopent-2-ene-1, 2-dicarboxylic acid dimethyl ester (2).

(1*R*, 2*S*)-4-oxo-cyclopentane-1, 2-dicarboxylic acid dimethyl ester (4.8 g, 23.8 mmol) and $CuBr_2$ (11.9 g, 53.2 mmol) were dissolved in dry THF (70 mL) and the mixture was refluxed for two hours at 90 °C. The formed CuBr was filtrated off and the organic phase was concentrated. $CaCO_3$ (2.7 g, 27.2 mmol) and DMF (70 mL) were added and the mixture was held at 100 °C for one hour. The dark brown mixture was poured over ice (35 g) and the formed precipitate was filtrated off. The aqueous layer was extracted with ethyl acetate (1 x 300mL + 3 x 150 mL). The organic phases were dried, filtrated and concentrated. Purification by flash chromatography (toluene/EtOAc 9:1) gave 2 (2.1 g, 45 %) as yellow crystals

Example 3



((1*S*,4*R*) & (1*R*,4*S*))-4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid dimethyl ester (3).

To a cold solution (-30 °C) of 2 (3.18 g, 16.1 mmol) dissolved in MeOH (23 mL), $NaBH_4$ (0.66 g, 17.5 mmol) was added. After nine minutes the excess of $NaBH_4$ was destroyed by adding brine (80 mL). The mixture was concentrated and extracted with ethyl acetate (4 x 80 mL). The organic phases were dried, filtrated and concentrated and gave 3 (3.0 g, 92 %) as a yellow oil.

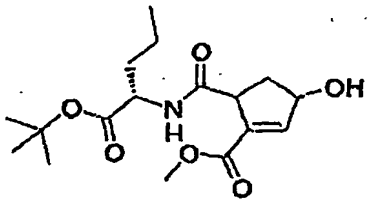
Example 4

(1*S*,4*R*) & (1*R*,4*S*)-4-hydroxy-cyclopent-2-ene-1,2-dicarboxylic acid 2-methyl ester (4).

To an ice-cold solution of 3 (3.4 g, 22 mmol) dissolved in dioxane and water (1:1, 110ml), LiOH (0.52 g, 22 mmol) was added. After two and a half hours the mixture was co-evaporated with toluene and methanol. Purification by flash chromatography (toluene/Ethyl acetate 3:1 + 1 % HOAc) gave the title compound (1.0 g, 27 %) as yellow-white crystals.

^{1}H-NMR (300 MHz, CD_3OD): δ 1.78-1.89 (m, 1H), 2.70-2.84 (m, 1H), 3.56-3.71 (m, 1H), 3.76 (s, 3H), 4.81-4.90 (m, 1H), 6.76-6.81 (m, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 38.0, 48.0, 52.4, 75.7, 137.0, 146.2, 165.0 178.4.

Example 5

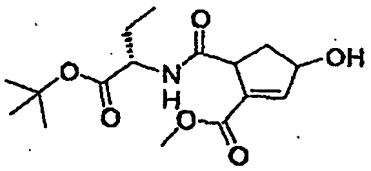


((3*S*,5*R*) & (3*R*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl (5).

To an ice cooled solution of 4 (0.20 g, 1.1 mmol) and 2-amino-pentanoic acid tert.butyl ester (0.24 g, 1.4 mmol) in DMF (7 mL), DIPEA (0.18 g, 1.4 mmol) and HATU (0.53 g, 1.4 mmol) were added. After two hours the solution was concentrated and purified using column chromatography (toluene/ethyl acetate 3:1). This gave the title compound as a yellow oil (0.22 g, 63 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.84-0.96 (m, 3H), 1.14-1.39 (m, 2H), [(1.44 & 1.49) s, 9H], 1.50-1.60 (m, 1H), 1.61-1.85 (m, 1H), 1.97-2.10 (m, 1H), 2.11-2.28 (m, 1H), 3.57-3.68 (m, 1H), [(3.73 & 3.76) s, 3H], 4.30-4.50 (m, 1H), 4.63-4.73 (m, 1H), 6.80-6.95 (m, 1H), 6.95-7.00 (m, 1H).

Example 6

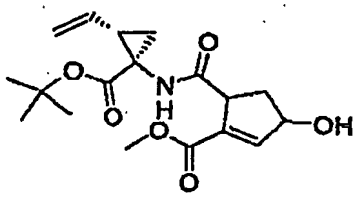


((3*S*,5*R*) & (3*R*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl ester (6).

Reaction of 4 (141 mg, 76 mmol) according to the method described for the preparation of 5 using L-2-amino-N-butyric acid tert.butyl ester instead of 2-amino-pentanoic acid tert.butyl ester gave the title compound as a slightly yellow oil (171 mg, 69 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89-0.98 (m, 3H), [(1.42 & 1.44) s, 9H], 1.60-1.78 (m, 1H), 1.79-1.95 (m, 1H), 1.99-2.11 (m, 1H), 2.18-2.30 (m, 1H), 3.58-3.65 (m, 1H), [3.75 & 3.78) s, 3 H], 4.22-4.39 (m, 1H), 4.61-4.66 (m, 1H), 6.77-6.90 (m, 1H), 6.91-6.92 (m, 1H).

Example 7

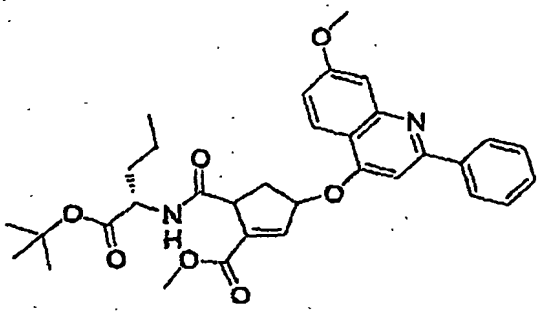


((3*S*,5*R*) & (3*R*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-hydroxy-cyclopent-1-enecarboxylic acid methyl ester (7).

Reaction of 4 (50 mg, 37 mmol) according to the method described for the preparation of 5 using (1R, 2S)-1-amino-2-vinyl-cyclopropane carboxylic acid *tert*.butyl ester instead of 2-amino-pentanoic acid *tert*.butyl ester provided the title compound as a slightly yellow oil (50 mg, 38 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ [(1.38 & 1.42) s, 9H], 1.75-1.83 (m, 1H), 2.00-2.21 (m, 3H), 3.55-3.63 (m, 1H), [(3.77 & 3.82) s, 3H], 4.20-4.38 (m, 1H), 4.65-4.80 (m, 1H), 5.13-5.20 (m, 1H), 5.22-5.38 (m, 1H), 5.60-5.82 (m, 1H), 6.95-6.96 (m, 2H).

Example 8

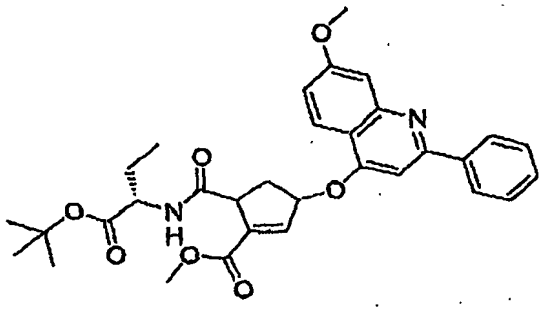


((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (8).

To an ice cooled solution of 5 (0.23 g, 0.67 mmol) in dry THF, 7-methoxy-2-phenyl-quinolin-4-ol (0.22 g, 0.88 mmol) and triphenylphosphine (0.23 g, 0.88 mmol) were added. Then DIAD (0.19 g, 0.92 mmol) was dissolved in THF (2 mL) and added dropwise to the solution. After one hour the mixture was concentrated and purified using flash chromatography (toluene/ethyl acetate 3:1). This gave the title compound as a white powder (0.30 g, 77 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0,88-1.00 (m, 3H), 1.18-1.43 (m, 2H), [(1.45 & 1.50) s, 9H], 1.53-1.65 (m, 1H), 1.66-1.85 (m, 1H), 2.29-2.43 (m, 1H), 3.10-3.25 (m, 1H), [(3.79 & 3.83) s, 3H], 3.97 (s, 3H), 4.05-4.20 (m, 1H), 4.38-4.50 (m, 1H), 6.03-6.13 (m, 1H), 6.65-6.90 (m, 1H), 7.04-7.18 (m, 3H), 7.40-7.56 (m, 4H), 8.00-8.12 (m, 3H).

Example 9

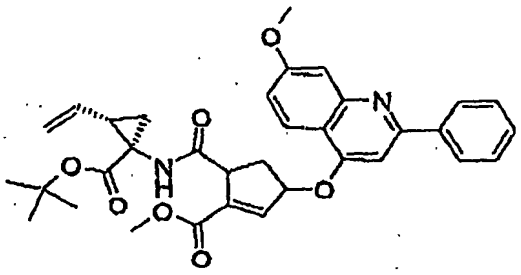


((3*R*,5*R*) & (3*S*,5*S*))--5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (9).

Reaction of 6 (132 mg, 40 mmol) according to the method described for the preparation of 8 gave the title compound as a yellow oil (137 mg, 61 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.83-0.98 (m, 3H), [(1.42 & 1.44) s, 9H], 1.65-1.78 (m, 1H), 1.80-1.97 (m, 1H), 2.30-2.40 (m, 1H), 3.05-3.20 (m, 1H), [(3.78 & 3.80) s, 3H], 3.94 (s, 3H), 3.95-4.01 (m, 1H), 4.38-4.44 (s, 1H), 6.05-6.15 (m, 1H), 6.80-6.94 (m, 1H), 7.02-7.15 (m, 3H), 7.38-7.55 (m, 4H), 7.97-8.18 (m, 3H).

Example 10

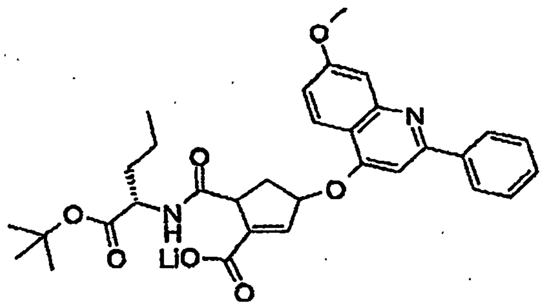


((3*R*,5*R*) & (3*S*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid methyl ester (10).

Reaction of 7 (41 mg, 116 mmol) according to the method described for the preparation of 8 provided the title compound as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.52-1.57 (m, 1H), 1.58 (m, 9H), 1.80-1.83 (m, 1H), 2.00-2.17 (m, 1H), 2.20-2.38 (m, 1H), 3.20-3.37 (m, 1H), 3.80 (s, 3H), 3.81-3-3.98 (m, 1H), 3.99 (s, 3H), 5.12-5.20 (m, 1H), 5.22-5.40 (m, 1H), 5.63-5.80 (m, 1H), 6.05-6-20 (m, 1H), 7.00-7.21 (m, 4H), 7.40-7.58 (m, 4H), 8.02-8.18 (m, 3H).

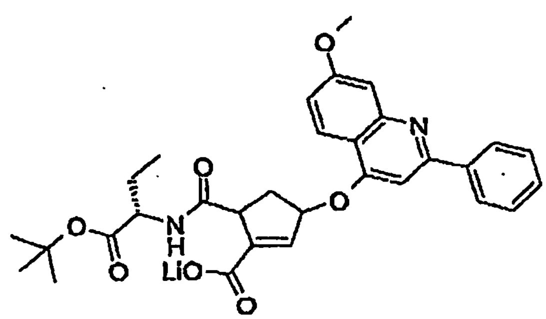
Example 11



((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-tert-Butoxycarbonyl-butylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (11).

The methyl ester 8 (0.35 g, 0.61 mmol) was dissolved in dioxane/water (1:1, 7ml) and LiOH (0.031 g, 1.3 mmol) was added. The reaction was stirred over night and then co-concentrated. This gave the lithium salt of 11 (0.32 g, 90 %) as a brown powder.

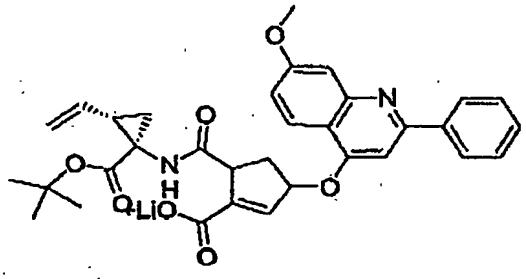
Example 12



((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (12)

Reaction of 9 (225 mg, 40 mmol) according to the method described for the preparation of 11 provided the title compound as a yellow salt (157 mg, 72 %).

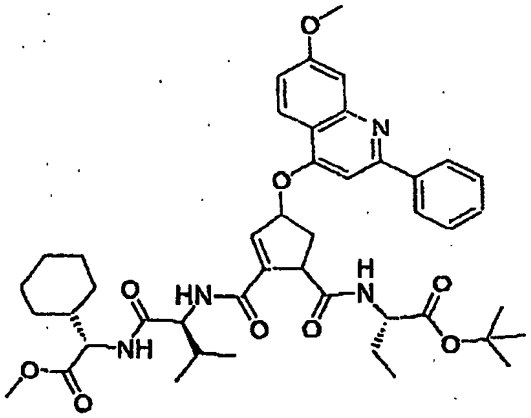
Example 13



((3*R*,5*R*) & (3*S*,5*S*))-5-((1*R*,2*S*)-1-*tert*-Butoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarboxylic acid (13).

Reaction of 10 (35 mg, 59 mmol) according to the method described for the preparation of 11 (33 mg, 97 %) provided the title compound as a yellow salt.

Example 14



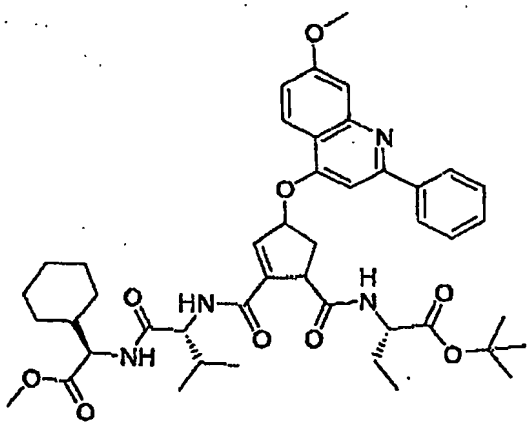
(*S*)-2-{[((1*S*,4*S*) & (1*R*,4*R*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (14).

The acid 12 (38.4 mg, 0.070 mmol) and (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester (26.6 mg, 0.098 mmol) were dissolved in DMF (1.5 mL) and

cooled in an ice-bath. DIPEA (17.1 µL, 0.098 mmol) and HATU (37.4 mg, 0.098 mmol) were added. After ninety minutes the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 6:1). Further purification was performed on HPLC (90 % MeOH + 0.2 % TEA). The diastereomeric mixture 14 was concentrated and gave a slightly yellow oil (20.6 mg, 37 %). After lyophilisation 14 was collected as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93-1.02 (m, 9H), 1.03-1.25 (m, 4H), 1.44 (s, 9H), 1.65-1.86 (m, 9H), 2.05-2.10 (m, 1H), 2.22-2.40 (m, 1H), 3.05-3.20 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.18-4.22 (m, 1H), 4.38-4.60 (m, 3H), 6.01-6.10 (m, 1H), 6.61-6.70 (m, 2H), 6.80-6.85 (m, 1H), 7.05-7.18 (m, 2H), 7.40-7.58 (m, 5H), 8.00-8.13 (m, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.7, 18.4, 19.2, [25.9 & 26.1], [28.2 & 28.5], 29.6, 32.0, 37.3, 41.0, 46.2, 50.7, 52.4, 54.4, 55.8, 57.2, 58.5, 82.0, 82.8, 98.4, 110.2, 118.4, 120.1, 123.2, 127.9, 128.2, 128.9, 129.5, 131.2, 135.1, 135.2, 142.7, 144.2, 161.6, 164.3, 164.7, 170.9, 171.4, 172.4. MALDI-TOF *m/z* 821.56 [(M +Na)$^+$ calcd for $C_{45}H_{58}N_4NaO_9^+$ 821.41].

Example 15

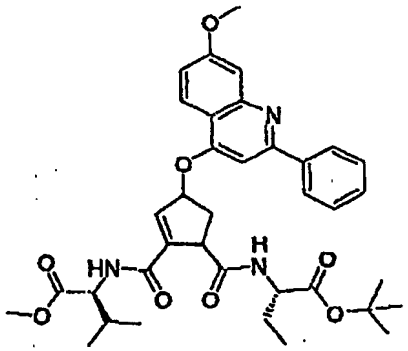


(*S*)-2-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (15).

Reaction of 12 (20 mg, 37 mmol) according to the method described for the preparation of 14 using (2-amino-3-methyl-butyrylamino)-(R)-cyclohexyl acetic acid methyl ester instead of (2-amino-3-methyl-butyrylamino)-(S)-cyclohexyl acetic acid methyl ester, gave the title compound (19 mg, 66 %) as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.91-0.98 (m, 3H), 0.99-1.10 (m, 6H), 1.11-1.38 (m, 4H), [(1.43 & 1.45) s, 9H], 1-45-1.94 (m, 9H), 2.05-2.18 (m, 1H), 2.22-2.40 (m, 1H), 3.16-3.24 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.04-4.18 (m, 1H), 4.36-4.57 (m, 3H), 6.00-6.08 (m, 1H), 6.13-6.21 (m, 1H), 6.62-6.70 (m, 1H), 6.81-6.85 (m, 1H), 7.05-7.18 (m, 3H), 7.41-7.57 (m, 4H), 8.02-8.13 (m, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 9.3, 18.2, 19.0, [25.5 & 25.9], [28.0 & 28.3], 29.4, 31.4, 32.1, 35.7, 40.7, 50.4, 52.2, 54.2, 55.5, 57.0, 58.2, 81.8, 82.4, 98.2, 107.5, 115.0, 118.1, 122.9, 127.6, 128.7, 128.8, 128.9, 129.2, 135.1, 140.4, 142.2, 151.4, 161.3, 163.9, 170.4, 170.9, 171.2, 172.0. MALDI-TOF *m/z* 821.60 [(M +Na)$^+$ calcd for $C_{45}H_{58}N_4NaO_9^+$ 821.41].

Example 16



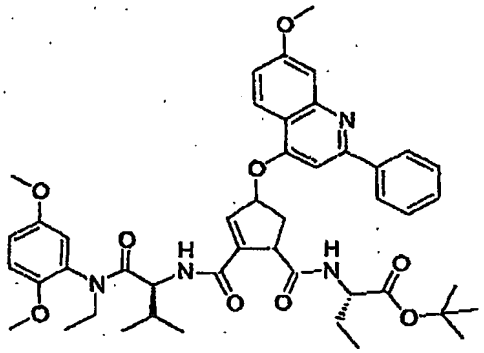
(*S*)-2-{[((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-*tert*-Butoxycarbonyl-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarbonyl]-amino}-3-methyl-butyric acid methyl ester (16).

Reaction of 12 (24 mg, 44 mmol) according to the method described for the preparation of 14 using D-valine methyl ester instead of (2-amino-3-methyl-

butyrylamino)cyclohexyl acetic acid methyl ester, gave the title compound (27 mg, 97 %) as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82-0.99 (m, 9H), [(1.42 & 1.44) s, 9H] 1.65-1.95 (m, 2H), 2.18-2.25 (m, 1H), 2.26-2.40 (m, 1H), 3.20-3.26 (m, 1H), 3.75 (s, 3H), 3.97 (s, 3H), 4.15-4.19 (m, 1H), 4.36-4.43 (m, 1H), 4.64-4.76 (m, 1H), 6.03-6.15 (m, 1H), 6.80-6.85 (m, 2H), 7.10-7.20 (m, 3H), 7.42-7.58 (m, 4H), 8.0-8.10 (m, 3H). ^{13}C-NMR (76.5 MHz, $CDCl_3$): δ 9.7, [18.2 & 19.1], 25.7, [28.1 & 28.2], 32.0, 35.6, 50.4, 52.4, 54.5, 55.7, 57.6, 81.7, 82.7, 98.4, 107.7, 115.2, 118.4, 123.2, 127.8, 129.0, 129.2, 129.5, 134.8, 135.0, 140.4, 142.5, 151.6, 159.6, [161.1 & 161.5], 164.6, 171.1, 172.2. MALDI-TOF *m/z* 682.51[(M +Na)$^+$ calcd for $C_{37}H_{45}N_3NaO_8^+$ 682.31].

Example 17



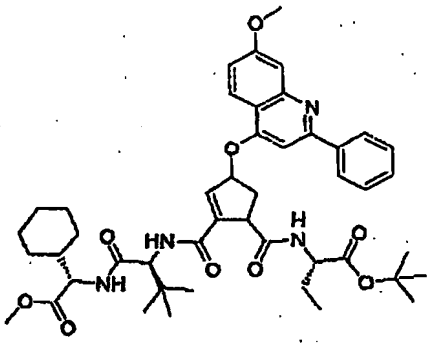
(*S*)-2-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-[(2,5-Dimethoxy-phenyl)-ethyl-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino)-butyric acid *tert*-butyl ester (17).

Compound 17 (28.6 mg, 59 %) was prepared from 12 (33 mg, 60 mmol) according to the method for the preparation of 14 using 2-amino-N-(2,5-dimethoxy-phenyl)-N-ethyl-3-methyl butyramide instead of (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester. This gave the title compound as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.76-0.95 (m, 9H) 1.05-1.18 (m, 3H), [(1.42 & 1.44) s, 9H],1.60-1.95 (m, 3H), 2.20-2.40 (m, 1H), 3.20-3.34 (m, 1H), 3.60-3.80 (m, 2H),

[3.62-3.65 (m, 3H)], [3.79-3.82 (m, 3H)], 3.98 (s, 3H), 4.02-4-18 (m, 1H), 4.30-4.44 (m, 2H), 6.05-6.18 (m, 1H), 6.60-6.63 (m, 1H), 6.77-6.80 (m, 2H), 6.85-6.93 (m, 2H), 7.12-7.20 (m, 2H), 7.35-7.60 (m, 5H), 8.02-8.20 (m, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ [9.6 & 9.7], [12.5 & 12.8], [17.1 & 17.5], [19.4 & 19.5], 25.6, [28.0 & 28.1], 32.4, 35.8, 43.0, 44.3, [50.2 & 50.3], 54.3, [54.8 & 55.0 & 55.2 & 55.5], [55.6 & 55.7 & 55.9 & 56.0], 81.7, 82.8, 98.4, 106.9, [112.4 & 112.5],113.7, 116.0, 115.2, 115.9, 116.3, 118.4, [123.0 & 123.1], [127.7 & 127.8], 128.8, 128.9, 129.5, 130.1, [134.1 & 134.2], 142.6, 149.1, 149.4, 153.4, 158.9,[161.4 & 161.6], [163.2 & 163.5], 170.9, [171.3 & 171.5], 172.3. MALDI-TOF *m/z* 831.62 [(M +Na)$^+$ calcd for $C_{46}H_{56}N_4NaO_9^+$ 831.39].

Example 18

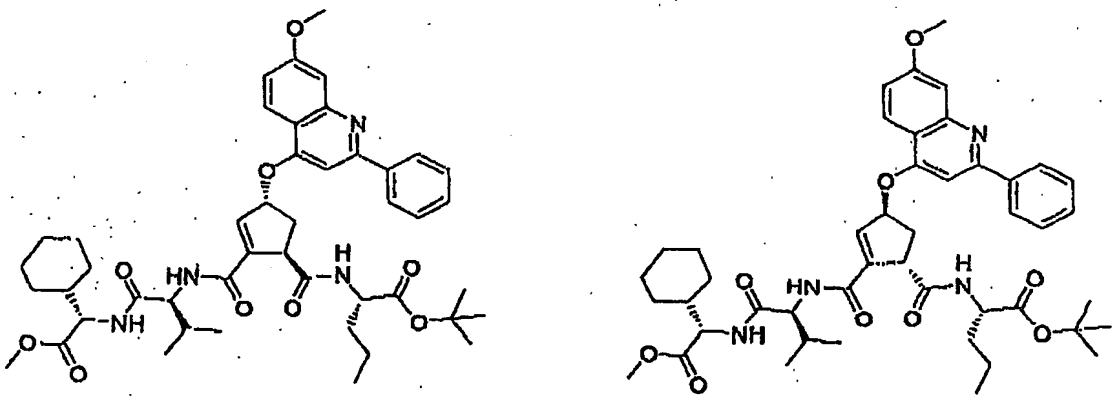


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid *tert*-butyl ester (18).

Compound 18 (16.1 mg, 26 %) was prepared from 12 (43.2 mg, 0.077 mmol) according to the method for the preparation of 14 using (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester instead of (2-amino-3-methyl-butyrylamino)-cyclohexyl acetic acid methyl ester. Flash column chromatography was performed in toluene/ethyl acetate 3:1 instead of 6:1: This gave the title compound as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.77-0.83 (m, 3H), [(0.92 & 0.93) s, 9H] 0.94-1.20 (m, 4 H), [(1.36 & 1.38) s, 9H], 1.42-1.76 (m, 8H), 2.20-2.38 (m, 1H), 2.81-2.96 (m, 1H), 3.20-3.22 (m, 1H), 2.78 (s, 3H), [(3.83 & 3.85) s, 3H], 3.97-4.02 (m, 1H), 4.17-4.21 (m, 1H), 4.22-4.37 (m, 2H), 5.85-5.97 (m, 1H), [6.76-6.78 (m, 0.5H)], [6.80-6.82 (m, 0.5H)], 6.98-7.05 (m, 3H), 7.23-7.41 (m, 6H), 7.82-7.99 (m, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ [9.4 & 9.5], [25.4 & 25.5], 25.8, [26.5 & 26.6], [27.9 & 28.0], [28.4 & 28.5], 29.3, [35.4 & 35.7], [36.0 & 36.4], [40.5 & 40.7], [50.2 & 50.5], [52.1 & 52.2],[54.1 & 54.3], 55.5, [57.0 & 57.3], [60.4 & 60.7], [81.8 & 82.0], [82.4 & 82.5] 98.1, 107.5, 115.0, 118.1, 123.0, 127.5, 128.7, 128.8, 129.2, 134.9, 135.8, 141.9, 142.5, 151.3, 159.4, [160.9 & 161.3], [163.7 & 163.9], [169.9 & 170.0] [170.0 & 171.3], [172.5 & 172.4]. MALDI-TOF *m/z* 835.68 [(M +Na)$^+$ calcd for $C_{46}H_{60}N_4NaO_9^+$ 835.43].

Example 19



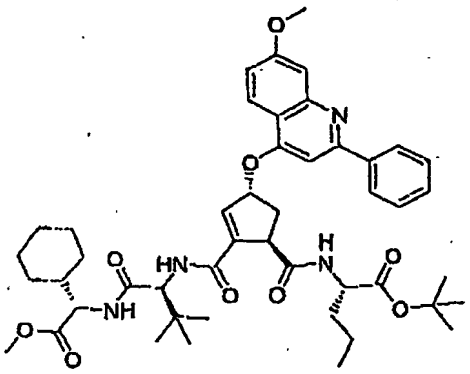
(*S*)-2-{[(1*R*,4*R*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (19a) and (*S*)-2-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (19b).

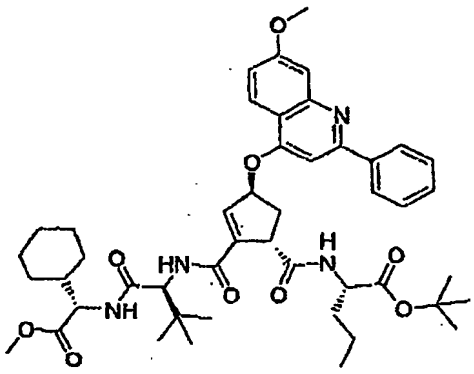
The acid 11 (0.051 g, 0.087 mmol) and (2-amino-3-methyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (0.054 g, 0.21 mmol) were dissolved in DMF (1.5 mL) and

cooled in an ice-bath. DIPEA (16 mg, 0.12 mmol) and HATU (47 mg, 0.13 mmol) were added. After two and a half hours the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 3:1). Further purification was performed on HPLC (90 % MeOH + 0.2 % TEA). This gave after co-concentration the two diastereomers 19a (9.4 mg, 13 %) and 19b (6.3 mg, 7 %) as slightly yellow syrups. After lyophilisation 19a and 19b were collected as white powders:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86-0.93 (m, 3H), 0.94-1.00 (m, 6H), 1.00-1.41 (m, 7H), 1.46 (s, 9H), 1.50-1.88 (m, 8H), 2.05-2.20 (m, 1H), 2.20-2.37 (m, 1H), 3.12-3.25 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.05-4.20 (m, 1H), 4.40-4.55 (m, 3H), 6.02-6.18 (m, 1H), 6.30 (d, J = 8.52 Hz, 1H), 6.63 (s, 1H), 6.76 (d, J = 8.51 Hz, 1H), 7.06-7.16 (m, 2H), 7.42-7.56 (m, 5H), 8.00-8.12 (m, 3H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 14.0, 18.4, 19.3, 26.1, 28.3, 28.5, 29.7, 31.9, 34.9, 36.0, 41.0, 50.7, 52.4, 53.3, 55.7, 57.2, 58.6, 82.0, 82.7, 98.4, 105.7, 107.7, 115.2, 118.4, 123.2, 125.3, 127.9, 129.0, 129.1, 135.1, 138.0, 142.4, 151.6, 159.4, 161.6, 164.3, 170.7, 171.2, 172.3. 19b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90-1.04 (m, 9H), 1.04-1.43 (m, 7H), 1.47 (s, 9H), 1.50-1.87 (m, 8H), 2.10-2.27 (m, 1H), 2.33-2.45 (m, 1H), 3.10-3.20 (m, 1H), 3.73 (s, 3H), 3.96 (s, 3H), 4.02-4.10 (m, 1H), 4.36-4.53 (m, 3H), 6.00-6.16 (m, 1H), 6.30 (d, J = 8.52 Hz, 1H), 6.73 (s, 1H), 6.86 (d, J = 7.96 Hz, 1H), 7.08-7.16 (m, 2H), 7.36-7.56 (m, 5H), 8.03-8.11 (m, 3H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 14.0, 18.6, 19.2, 26.1, 28.2, 28.7, 29.7, 34.5, 36.1, 36.6, 40.8, 50.5, 52.4, 53.4, 55.7, 57.3, 59.1, 64.8, 82.3, 98.4, 105.8, 107.8, 115.3, 118.4, 123.2, 127.8, 129.0, 129.4, 135.2, 142.2, 144.9, 151.0, 151.6, 159.2, 164.3, 164.3, 170.2, 171.6, 171.9

Example 20





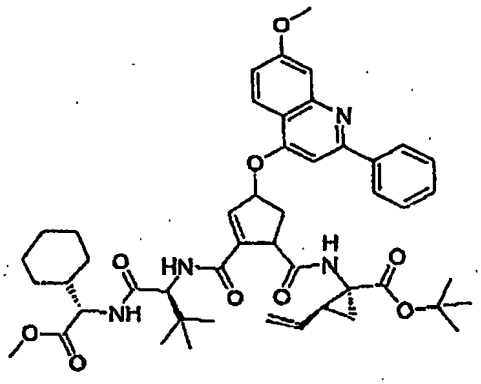
(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (20a) and (*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (20b).

Method A: The carboxylic acid 11 (57 mg, 0.10 mmol) was dissolved in warm (50 °C) dry THF (2 mL). (2-Amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (50 mg, 0.12 mmol), DIPEA (30 mg, 0.23 mmol), DCC (25 mg, 0.12 mmol) and HOBt (17 mg, 13 mmol) were added. After two hours the mixture was concentrated and added to a short column (toluene/Ethyl acetate 1:3 + 3 % AcOH). Then it was further purified on HPLC using 90 % MeOH + 0.2 % TEA. The diastereomeric products were not separated. After HPLC the solution was co-concentrated with toluene and methanol to give 20 (28 mg, 34%).

Method B: To an ice-cold solution of 11 (60 mg, 0.10 mmol) and (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (42 mg, 0.15 mmol) DIPEA (19 mg, 0.15 mmol) and HATU (62 mg, 0.16 mmol) were added. After two and a half hours the mixture was concentrated and purified using column chromatography. (toluene/Ethyl acetate 3:1). The diastereomeric mixture was separated using HPLC (90 % MeOH + 0.2 % TEA). This gave 20a (6 mg, 6 %) and 20b (9 mg, 10%).

20a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82-0.90 (m, 3H), 1.01 (s, 9H), 1.05-1.40 (m, 7H), 1.46 (s, 9H), 1.50-1.80 (m, 8H), 2.20-2.35 (m, 1H), 3.07-3.25 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.11 (d, *J* = 7.96 Hz, 1H), 4.38-4.52 (m, 3H), 6.03-6.12 (m, 1H), 6.24 (d, *J* = 8.79 Hz, 1H), 6.63 (s, 1H), 6.82 (d, *J* = 9.06 Hz, 1H), 7.07-7.27 (m, 2H), 7.36 (d, *J* = 7.96 Hz, 1H), 7.41-7.55 (m, 4H), 8.01-8.10 (m, 3H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 14.0, 18.8, 26.1, 26.8, 28.2, 28.6, 29.6, 34.9, 35.6, 36.2, 40.9, 50.7, 52.4, 53.3, 55.7, 57.3, 60.8, 82.0, 82.7, 98.4, 105.2, 107.7, 115.2, 118.4, 123.2, 127.9, 129.0, 129.4, 131.1, 135.1, 138.4, 142.4, 153.3, 159.6, 161.6, 164.2, 170.1, 171.3, 172.2. 20b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90-0.98 (m, 3H), 1.04 (s, 9H), 1.08-1.40 (m, 7H), 1.44 (s, 9H), 1.55-1.90 (m, 8H), 2.20-2.38 (m, 1H), 3.10-3.22 (m, 1H), 3.73 (s, 3H), 3.97 (s, 3H), 4.02-4.15 (m, 1H), 4.35-4.48 (m, 3H), 6.00-6.08 (m, 1H), 6.72 (s, 1H), 6.90 (d, *J* = 9.06 Hz, 1H), 7.09-7.20 (m, 3H), 7.44-7.55 (m, 5H), 8.03-8.11 (m, 3H).

Example 21



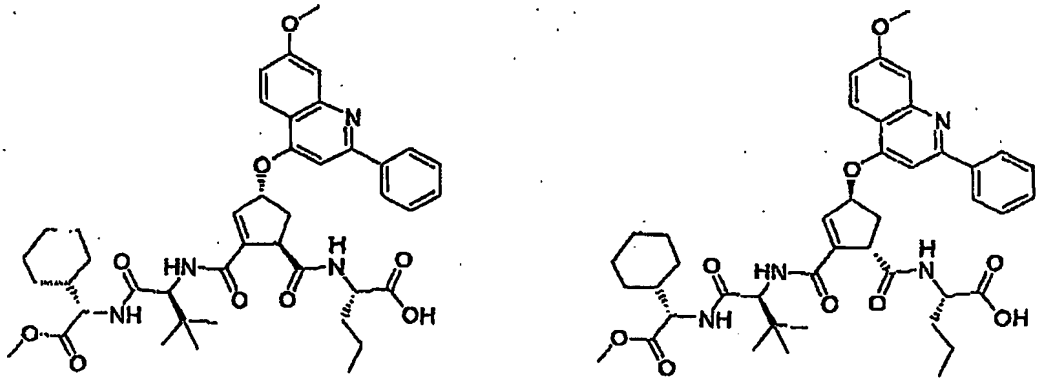
(1*R*,2*S*)-1-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-{((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid *tert*-butyl ester (21).

The acid 13 (35 mg, 0.060 mmol) and (2-amino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (22 mg, 0.080 mmol) were dissolved in dry THF

(1.5 mL) and warmed to 50 °C. HOBt (11 mg, 0.080 mmol) and DCC (31 mg, 0.15 mmol) were added. After one hour the mixture was co-concentrated with toluene and methanol and then purified by flash column chromatography (toluene/ethyl acetate 1:1). Further purification was performed on HPLC (80 % MeOH + 0.2 % TEA. The diastereomeric mixture 21 was concentrated and gave a slightly yellow oil (26.4 mg, 53 %). After lyophilisation 21 was collected as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$): δ [(0.98 & 1.00), s, 9H], 1.01-1.38 (m, 5H), [(1.39 & 1.40) s, 9H], 1.52-1.63 (m, 4H), 1.65-1.80 (m, 4H), 1.90-2.05 (m, 1H), 2.20-2.40 (m, 1H), 3.02-3.20 (m, 1H), [(3.66 & 3.67) s, 3H), 3.98 (s, 3H), 3.99-4.02 (m, 1H), 4.30-4.45 (m, 2H), 5.05-5.11 (m, 1H), 5.20-5.30 (m, 1H), 5.60-5.81 (m, 1H), 6.03-6.17 (m, 1H), 6.77-6.82 (m, 1H), 6.95-7.22 (m, 5H), 7.40-7.50 (m, 4H), 8.01-8.10 (m, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 22.3, [25.7 & 25.8], [26.4 & 26.5], [28.0 & 28.4] 29.2, 32.7, 33.3, [35.3 & 35.4], 36.0, [40.2 & 40.3], 40.7, 52.0, 55.4, [57.2 & 57.4] [60.4 & 60.5], [87.6 & 87.7], [82.3 & 82.5], 98.4, 107.0, 114.9, [117.4 & 117.5], 118.1, 122.9, 127.6, 128.6,128.9, 129.2, [133.6 & 133.8], 135.9, 136.9, 140.1, [141.4 & 141.6], 151.1, 159.6, [160.9 & 161.3], [164.2 & 164.6], 168.9, 170.3, [172.1 & 172.6]. MALDI-TOF *m/z* 859.77 [(M +Na)$^+$ calcd for $C_{48}H_{60}N_4NaO_9^+$ 859.43].

Example 22



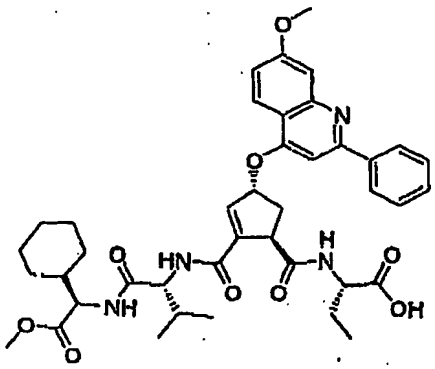
(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid (22a) and

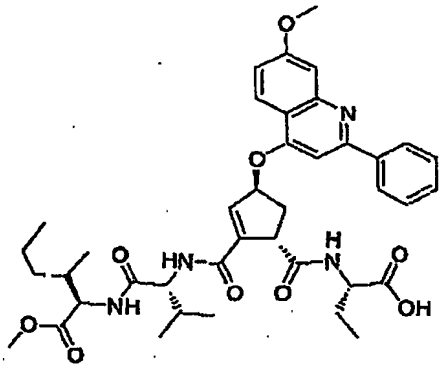
(*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid (22b).

The tert.butyl ester 20 (28 mg, 0.034 mmol), TES (8.7 mg, 0.075 mmol), DCM (1 mL) and TFA (1 mL) were mixed in a round bottomed flask. Two hours later the mixture was concentrated and the diastereomers were separated on HPLC using 65 % MeOH + 0.2 % TEA as mobile phase. This gave 22a (15 mg, 55 %) and 22b (12 mg, 45 %) as slightly yellow syrups. After lyophilisation the title compounds were collected as white powders.

22a: $[\alpha]^{22}D$ + 155.8; ^{1}H-NMR (300 MHz, CD_3OD): δ 0.90-0.97 (m, 3H), 1.03 (s, 9H), 1.05-1.50 (m, 7H), 1.50-1.80 (m, 8H), 2.43-2.55 (m, 1H), 2.77-2.90 (m, 1H), 3.68 (s, 3H), 3.96 (s, 3H), 4.20-4.30 (m, 2H), 4.31-4.40 (m, 1H), 4.45-4.50 (m, 1H), 6.03-6.11 (m, 1H), 6.98 (s, 1H), 7.12-7.19 (m, 1H), 7.36 (s, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.50-7.60 (m, 3H), 8.03-8.10 (m, 3H): ^{13}C-NMR (75.5 MHz, CD_3OD): δ 13.1, 19.1, 26.1, 28.7, 28.9, 29.6, 34.3, 34.8, 35.9, 40.1, 50.8, 51.2, 54.8, 55.0, 57.9, 60.7, 83.5, 99.1, 106.0, 115.2, 118.2, 123.3, 127.8, 128.0, 128.7, 128.8, 129.7, 135.2, 139.8, 143.7, 150.6, 160.1, 162.2, 165.2, 171.7, 172.2, 173.4. 22b: $[\alpha]^{22}D$ -72,3; ^{1}H-NMR (300 MHz, CD_3OD): δ 0.90-0.97 (m, 3H), 1.02 (s, 9H), 1.07-1.35 (m, 7H), 1.53-1.90 (m, 8H), 2.46-2.61 (m, 1H), 2.76-2.88 (m, 1H), 3.69 (s, 3H), 3.96 (s, 3H), 4.15-4.35 (m, 2H), 4.37-4.41 (m, 1H), 4.42-4.47 (m, 1H), 6.02-6.12 (m, 1H), 7.02 (s, 1H), 7.16 (dd, *J* = 2.47, 9.34 Hz, 1H), 7.32 (s, 1H), 7.40 (d, *J* = 2.47 Hz, 1H), 7.48-7.58 (m, 3H), 8.03-8.12 (m, 3H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 13.0, 18.8, 25.9, 26.0, 28.8, 29.4, 34.2, 34.8, 36.3, 39.9, 48.8, 50.5, 51.1, 54.8, 57.9, 60.5, 82.8, 99.0, 106.0, 115.1, 118.2, 123.1, 127.8, 127.9, 128.7, 129.0, 129.5, 136.7, 139.8, 142.8, 150.6, 160.1, 162.0, 162.2, 164.7, 172.1, 173.5.

Example 23



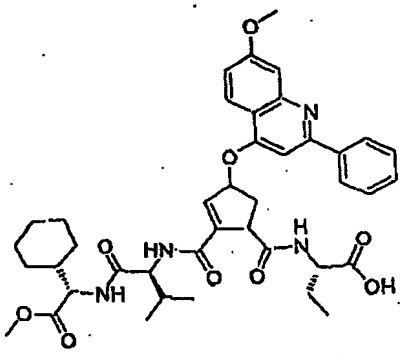


(*S*)-2-{[(1*R*,4*R*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (23a) and (*S*)-2-{[(1*S*,4*S*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (23b).

Compound 23a (6.6 mg, 50 %) and compound 23b (1.3 mg, 10 %) were prepared from 15 (14 mg, 0.018 mmol) according to the method for the preparation of 22a and 22b. This gave the title compounds as white powders.

23a: ^{1}H-NMR (300 MHz, CD_3OD): 0.88-1.02 (m, 9H), 1.02-1.40 (m, 7H), 1.55-1.97 (m, 6H), 2.01-2.10 (m, 1H), 2.38-2.52 (m, 1H), 2.88-3.00 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.08-4.20 (m, 1H), 4.22-4.40 (m, 3H). 6.03-6.18 (m, 1H), 6.86-6.99 (m, 1H), 7.08-7.20 (m, 1H), 7.23 (s, 1H), 7.40-7.43 (m, 1H), 7.45-7.70 (m, 3H), 8.02-8.20 (m, 3H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 9.0, 17.6, 18.2, 24.5, 25.3, 28.1, 28.8, 30.9, 35.4, 39.4, 49.6, 51.1, 54.7, 57.2, 58.0, 82.4, 98.5, 105.5, 114.5, 117.7, 122.7, 127.2, 127.3, 128.2, 129.0, 135.6, 136.4, 141.7, 149.9, 159.5, 161.2, 161.4, 164.0, 171.0, 171.7, 172.4. 23b: ^{1}H-NMR (300 MHz, CD_3OD): δ 0.9-1.20 (m, 9H), 1.21-1.53 (m, 7H), 1.55-1.93 (m, 6H), 2.05-2.20 (m, 1H), 2.41-2.50 (m, 1H), 2.96-3-05 (m, 1H), 3.77 (s, 3H), 4.00 (s, 3H), 4.05-4.40 (m, 4H), 6.05-6.18 (m, 1H), 6.90-6.95 (m, 1H), 7.05-7.22 (m, 2H), 7.50-7.65 (m, 4H), 8.01-8.16 (m, 3H).

Example 24

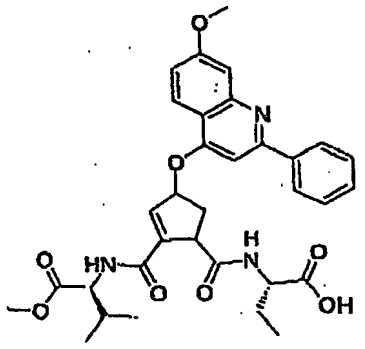


(*S*)-2-{[((1*R*,4*R*) & (1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Carboxy-cyclohexyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino)-butyric acid (24).

The tert.butyl ester 14 (13.4 mg, 0.017 mmol), TES (4.83 mg, 0.042 mmol), DCM (2 mL) and TFA (2 mL) were mixed in a round bottomed flask. One hour later the mixture was concentrated and purified by HPLC using 65 % MeOH + 0.2 % TEA as mobile phase. This gave 24 (4.3 mg, 34 %) as a slightly yellow syrup. After lyophilisation 24 was collected as a white powder.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.91-0.99 (m, 9H), 1.00-1.28 (m, 4H), 1.55-1.78 (m, 9H), 1.92-1.95 (m, 1H), 2.00-2.05 (m, 1H), 2.93-3.01 (m, 1H), 3.75 (s, 3H), 3.97 (s, 3H), 4.10-4.40 (m, 4H), 6.05-6.15(m, 1H), 6.88-6.94 (m, 1H), 7.05-7.10 (m, 2H), 7.41-7.43 (m, 1H), 7.44-7.55 (m, 2H), 8.62-8.68 (m, 1H), 8.69-8.79 (m, 1H), 7.97-8.05 (m, 2H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 9.2, 18.5, 25.5, [29.0 & 29.2], [30.0 & 30.5], 35.3, 37.7, 39.7, 46.2, 50.0, [51.4 & 51.6], 53.6, 55.1, 57.1, 58.4, 83.1, 98.9, 104.9, 114.6, 118.3, 123.0, 123.4, 127.5, 128.4, 128.5, 129.7, 135.0, 142.1, 145.7, 146.2, 159.2, 161.9, 164.3, 171.5, 171.9, 172.2. MALDI-TOF *m/z* 791.27 [(M +K)$^+$ calcd for $C_{42}H_{48}KN_4O_9^+$ 791.31].

Example 25

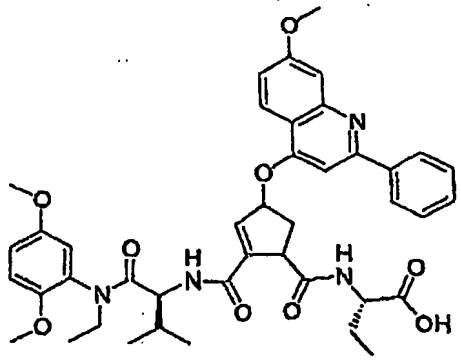


(*S*)-2-{[((3*R*,5*R*) & (3*S*,5*S*))-5-((*S*)-1-Carboxy-propylcarbamoyl)-3-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-1-enecarbonyl]-amino}-3-methyl-butyric acid methyl ester (25).

Compound 25 (8.0 mg, 60 %) was prepared from 16 (13.8 mg, 0.022 mmol) according to the method for the preparation of 24 which gave the title compound as a white powder.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.83-1.02 (m, 9H), 1.68-1.80 (m, 1H), 1.82-2.02 (m, 1H), 2.10-2.22 (m, 1H), 2.40-2.60 (m, 1H), 2.81-2.95 (m, 1H), 3.75 (s, 3H), 4.00 (s, 3H), 4.18-4.22 (m, 1H), 4.27-4.40 (m, 2H), 6.05-6.12 (m, 1H), 6.99-7.02 (m, 1H), 7.16-7.21 (m, 1H), 7.38 (s, 1H), 7.40-7.43 (m, 1H), 7.48-7.61 (m, 3H), 7.98-8.12 (m, 3H).

Example 26

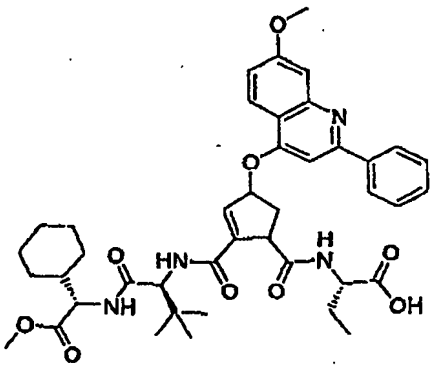


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[(2,5-Dimethoxy-phenyl)-ethyl-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (26).

Compound 26 (5.7 mg, 36 %) was prepared from 17 (16.7 mg, 0.021 mmol) according to the method for the preparation of 24 which gave the title compound as a white powder.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.75-0.81 (m, 6H), 0.82-0.98 (m, 3H), 1.00-1.10 (m, 3H), 1.60-2.00 (m, 3H), 2.40-2.56 (m, 1H), 2.80-2.88 (m, 1H), 3.18-3.24 (m, 1H), 3.40-3.46 (m, 1H), [3.67-3.80 (m, 6H)], 3.97 (s, 3H), 4.10-4.20 (m, 1H), 4.21-4.40 (m, 2H), 6.02-6.17(m, 1H), 6.75-6.82 (m, 1H), 6.84-7.01 (m, 3H), 7.10-7.20 (m, 1H), 7.30-7.37 (m, 1H), 7.40-7.43 (m, 1H), 7.50-7.60 (m, 3H), 8.00-8.17 (m, 3H). ^{13}C-NMR (75.6 MHz, CD_3OD): δ 9.6, [11.8 & 12.0], [17.2 & 17.4], 18.9, 25.0, 32.3, 35.7, 43.3, 44.2, [50.3 & 50.5], [54.5 & 54.8 & 54.9 & 55.0], [55.1 & 55.2 & 55.3 & 56.0] ,58.7, 83.6, 99.3, 105.5, [112.5 & 112.7], 114.3, [15.1 & 115.2], 115.7, 116.1, 118.4, [123.3 & 123.4], 125.2, [128.0 & 128.1, 128.8, 129.1, 129.8, [135.1 & 135.3], 139.2, [143.3 & 144.4], 149.2, [149.6 & 149.9], 153.8, 159.9, 162.4, [163.9 & 164.5], 172.1, 172.8, [173.6 & 173.7]. MALDI-TOF *m/z* 775.30 [(M +Na)$^+$ calcd for $C_{42}H_{48}N_4NaO_9^+$ 775.33].

Example 27

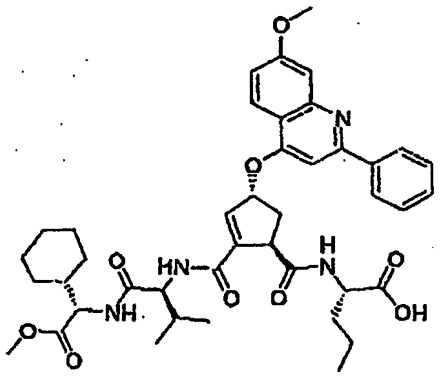


(*S*)-2-{[((1*R*,4*R*) &(1*S*,4*S*))-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-butyric acid (27).

Compound 27 (6.0 mg, 72 %) was prepared from 18 (8.6 mg, 0.011 mmol) according to the method for the preparation of 24. Purification by HPLC (60 % methanol + 0.2 % TEA) gave the title compound as a white powder.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.88-0.95 (m, 3H), 0.96 (s, 9H), 0.97-1.24 (m, 4H), 1.57-1.62 (m, 3H), 1.68-1.78 (m, 4H), 1.79-1.99 (m, 1H), 2.35-2.44 (m, 2H), 2.85-2.98 (m, 1H), [(3.67 & 3.69) s, 3H], 3.94 (s, 3H), 4.10-4.20 (m, 1H), 4.30-4.40 (m, 3H), 6.00-6.09 (m, 1H), [6.80-6.82 (m, 0.5H)] [6.85-6.87 (m, 0.5H)], 7.05-7.19 (m, 2H), 7.38-7.55 (m, 4H), 7.95-8.07 (m, 3H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ [9.1 & 9.2], [24.7 & 24.9], [25.4 & 25.5], [25.9 & 26.0], [28.3 & 28.4], 28.9, [34.8 & 34.9], [35.6 & 35.9], [39.6 & 39.7], [49.9 & 50.1], [51.4 & 51.2], [53.9 & 54.0] 55.0, [57.2 & 57.4], 60.0, [82.1 & 82.5], 98.6, 106.2, 114.7, 117.8, 122.7, 127.5, 127.7, [128.4 & 128.5], 129.1, 135.3, 136.3, 141.6, 142.0, 150.5, 159.8, [161.0 & 161.3] [164.0 & 164.1], [171.6 & 171.9], [172.2 & 172.3], [173,0 & 173.2].MALDI-TOF *m/z* 779.43 [(M +Na)$^+$ calcd for $C_{42}H_{52}N_4NaO_9^+$ 779.36].

Example 28

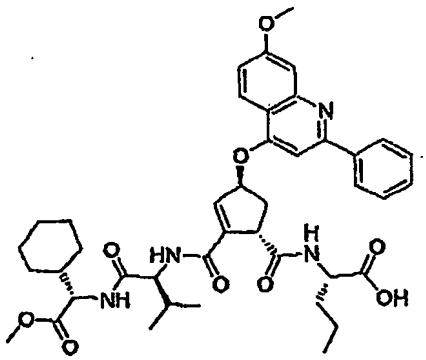


(*S*)-2-{[(1*R*,4*R*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (28).

The tert.butyl ester 19a (7.6 mg, 0.0094 mmol) and TES (2.4 mg, 0.021 mmol) were dissolved in DCM (1 mL) and the mixture was cooled in an ice-bath. TFA (1 mL) was added. After two hours the mixture was concentrated and purified on HPLC using 60 % MeOH + 0.2 % TEA as mobile phase. This gave 28 (6.1 mg, 86 %) as a slightly yellow syrup. After lyophilisation the title compound was collected as white powder.

^{1}H-NMR (300 MHz, CD_3OD + CDCl3 (1:1)): δ 0.90-1.00 (m, 9H), 1.00-1.30 (m, 7H), 1.50-1.90 (m, 8H), 2.00-2.10 (m, 1H), 2.40-2.50 (m, 1H), 2.85-2.98 (m, 1H), 3.65-3.72 (s, 3H), 3.99 (s, 3H), 4.15-4.22 (m, 1H), 4.24-4.35 (m, 2H), 4.38-4.44 (m, 1H), 6.10-6.20 (m, 1H), 6.95-6.96 (m, 1H), 7.16-7.23 (m, 1H), 7.31 (s, 1H), 7.42 (d, *J* = 2.47 Hz, 1H), 7.53-7.72 (m, 3H), 7.97-8.16 (m, 3H); ^{13}C-NMR (75.5 MHz, CD_3OD + $CDCl_3$ 1:1): δ 13.5, 18.3, 19.0, 26.0, 29.0, 29.7, 31.0, 34.1, 35.8, 40.2, 51.9, 55.9, 57.7, 58.9, 63.5, 68.4, 84.0, 99.6, 104.8, 105.7, 115.1, 119.0, 123.7, 128.1, 128.9, 129.1, 130.4, 131.3, 135.3, 138.0, 142.9, 159.5, 162.8, 164.8, 172.2, 172.2, 172.4

Example 29

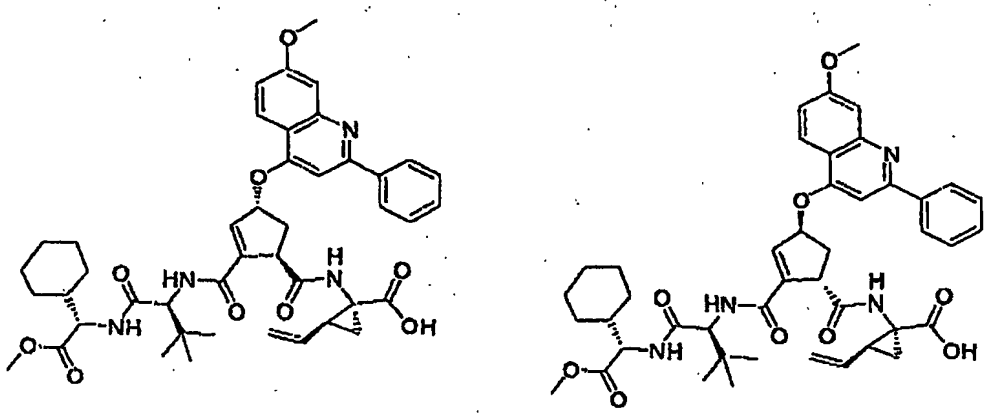


(*S*)-2-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-pentanoic acid tert-butyl ester (29).

Compound 29 (1.3 mg, 26 %) was prepared from 19b (5.3 mg, 0.065 mmol) according to the method for the preparation of 28. This gave the title compound as a white powder.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.85-1.00 (m, 9H), 1.00-1.23 (m, 7H), 1.50-1.78 (m, 8H), 2.05-2.23 (m, 1H), 2.50-2.66 (m, 1H), 2.70-2.85 (m, 1H), 3.69 (s, 3H), 3.92 (s, 3H), 4.02-4.16 (m, 1H), 4.20-4.25 (m, 1H), 4.35-4.40 (m, 2H), 6.09 (m, 1H), 7.00 (s, 1H), 7.12-7.18 (dd, *J* = 2.47, 2.19 Hz, 1H), 7.30 (s, 1H), 7.40 (d, *J* = 2.42 Hz, 1H), 7.48-7.74 (m, 3H), 8.03-8.10 (m, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 11.7, 16.5, 17.0, 24.4, 27.2, 27.9, 29.0, 29.1 37.5, 41.8, 49.7, 50.5, 53.3, 56.3, 63.5, 66.5, 81.0, 100.3, 101.0, 105.7, 113.6, 121.6, 126.3, 127.1, 127.9, 130.1, 131.4, 135.6, 138.7, 141.1, 150.4, 160.2, 160.5, 165.3, 173.0, 173.6, 173.7

Example 30

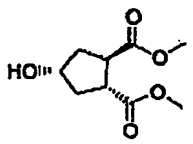


(1*R*,2*S*)-1-{[(1*R*,4*R*)-2-{(*S*)-1-{((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino)-2-vinyl-cyclopropanecarboxylic acid (30a) and 1*R*,2*S*)-1-{[(1*S*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopent-2-enecarbonyl]-amino}-2-vinyl-cyclopropane-carboxylic acid (30b).

Compound 30a (6.3 mg, 49 %) and compound 30b (5.6 mg, 43 %) were synthesized from 21 (13.8 mg, 0.0016 mmol) according to the method of the preparation of 22a and 22b. 30a and 30b: White powder.

30a: ^{1}H-NMR (300 MHz, CD_3OD): δ 1.02 (s, 9H), 1.03-1.43 (m, 5H), 1.61-1.95 (m, 8H), 2.11-2.21 (m, 1H), 2.43-2.58 (m, 1H), 2.97-3.04 (m, 1H), 3,78 (s, 3H), 4.01 (s, 3H), 4.02-4.17 (m, 1H), 4.25-4.40 (m, 2H), 5.10-5-20 (m, 1H), 5.27-5.40 (m, 1H), 6.77-6.94 (m, 1H), 6.10-6.20 (m, 1H), 6.97 (s, 1H), 7.18 (dd, *J* = 2.5, 9.2 Hz, 1H), 7.22 (s, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.52-7.65 (m, 3H), 8.00-8.18 (m, 3H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 13.5, 25.3, 25.7, 28.3, 28.7, 29.0, 32.8, 34.6, 35.3, 39.3, 49.7, 51.1, 54.6, 57.2, 59.8, 82.1, 98.4, 105.8, 114.5, 116.3, 117.6, 122.6, 127.2, 128.1, 128.2, 128.8, 130.2, 133.7, 136.0, 139.5, 141.5, 150.3, 159.7, 161.0, 161.2, 163,4, 171.6, 172.5. MALDI-TOF *m/z* 803.56 [(M +Na)$^+$ calcd for $C_{44}H_{52}N_4NaO_9^+$ 803.36].
30b: ^{1}H-NMR (300 MHz, CD_3OD): δ 1.03 (s, 9H), 1.04-1.42 (m, 5H), 2.60-2.90 (m, 8H), 2.17-2.22 (m, 1H), 2.40-2.55 (m, 1H), 2.96-3.10 (m, 1H), 3.77 (s, 3H), 4.01 (s, 3H), 4.05-4.16 (m, 1H), 4.30-4.40 (m, 2H), 5.15-5.20 (m, 1H), 5.25-5.40 (m, 1H), 5.78-5.95 (m, 1H), 6.10-6.20 (m, 1H), 6.98 (s, 1H), 7.17 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.26 (s, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.50-7.65 (m, 3H), 8.03-8.28 (m, 3H). ^{13}C-NMR (75.5 MHz, CD_3OD): δ 13.7, 26.0, 26.3, 28.8, 29.4, 29.6, 34.0, 35.2, 35.8, 40.1, 50.6, 51.7, 55.3, 57.8, 60.6, 83.0, 99.1, 106.3, 115.2, 117.0, 118.3, 123.2, 127.9, 128.0, 128.8, 129.6, 130.6, 134.4, 136.1, 140.0, 142.5, 150.8, 160.3, 161.8, 162.0, 165.7, 172.3, 173.0

Example 31



trans-(3*R*,4*R*)-Bis(methoxycarbonyl)cyclopentanol (31).

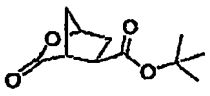
Sodium borohydride (1.11 g, 0.029 mol) was added to a stirred solution of (1R, 2S)-4-oxo-cyclopentane1,2-dicarboxylic acid dimethyl ester (4.88 g, 0.0244 mol) in methanol (300 mL) at 0 °C. After 1 h the reaction was quenched with 90 mL brine, concentrated and extracted with ethyl acetate. The organic phases were pooled, dried, filtered and concentrated. The crude product was purified by flash column chromatography (toluene/ethyl acetate 1:1) to give 31 (3.73 g, 76%) as a yellow oil.

Example 32

3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid (32).

Sodium hydroxide (1M, 74 mL, 0.074 mol) was added to a stirred solution of 31 (3.73 g, 0.018 mol) in methanol (105 mL) at room temperature. After 4 h, the reaction mixture was neutralized with 3M HCl, evaporated and co-evaporated with toluene several times. Pyridine (75 mL) and Ac_2O (53 mL) were added and the reaction mixture was allowed to shake overnight at room temperature. The mixture was then co-evaporated with toluene and purified by flash column chromatography (ethyl acetate + 1% acetic acid) to give 32 (2.51 g, 88%) as a yellow oil.

Example 33



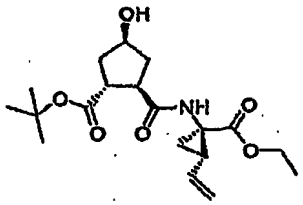
3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid *tert*-butyl ester (33)

DMAP (14 mg, 0.115 mmol) and Boc_2O (252 mg, 1.44 mmol) was added to a stirred solution of 32 (180 mg, 1.15 mmol) in 2 mL CH_2Cl_2 under inert argon atmosphere at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was concentrated and the crude product was purified

by flash column chromatography (toluene/ethyl acetate gradient 15:1, 9:1, 6:1, 4:1, 2:1) to give 33 (124 mg, 61%) as white crystals.

^{1}H-NMR (300 MHz, CD_3OD) δ 1.45 (s, 9H), 1.90 (d, J = 11.0 Hz, 1H), 2.10-2.19 (m, 3H), 2.76-2.83 (m, 1H), 3.10 (s, 1H), 4.99 (s, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD) δ 27.1, 33.0, 37.7, 40.8, 46.1, 81.1, 81.6, 172.0, 177.7.

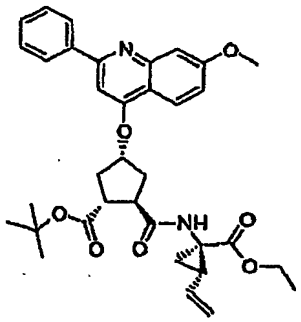
Example 34



(1*R*,2*R*,4*S*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid *tert*-butyl ester (34)

Compound 33 (56 mg, 0.264 mmol) was dissolved in dioxane/ water 1:1 (5 mL) and the mixture was cooled to 0 °C. 1 M lithium hydroxide (0.52 mL, 0.520 mmol) was added and the mixture was stirred at 0 °C for 45 minutes, after which the mixture was neutralized with 1M hydrochloric acid and evaporated and coevaporated with toluene. The residue was dissolved in DMF (5 mL) and (1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride (60 mg, 0.313 mmol) and diisopropylethylamine (DIEA) (138 µL, 0.792 mmol) were added and the solution was cooled to 0 °C. HATU (120 mg, 0.316 mmol) was added and the mixture was stirred for 0.5 h at 0 °C and for an additional 2 h at room temperature. The mixture was then evaporated and extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification by flash column chromatography (toluene/ EtOAc 1:1) provided compound 34 (86 mg, 89 %) as a colorless oil.

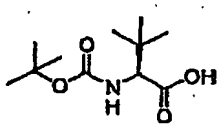
Example 35



(1*R*,2*R*,4*R*)-2-((1*R*,2*S*)-1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid *tert*-butyl ester (35)

Compound 34 (73 mg, 0.199 mmol) was dissolved in dry THF (4 mL) and 2-phenyl-7-methoxy-4-quinolinol (86 mg, 0.342 mmol) and triphenylphosphine (141 mg, 0.538 mmol) were added. The mixture was cooled to 0°C and DIAD (0.567 mmol) dissolved in 1 mL THF was added dropwise. The mixture was stirred for 48 h at room temperature. The solvent was evaporated and the crude product was purified by flash column chromatography gradient elution (toluene/ EtOAc 9:1, 6:1, 4:1) to give compound 35 (81 mg, 68 %).

Example 36



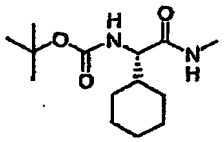
Boc-L-*tert*-leucine-OH (36).

Triethylamine (890 µL, 6.40 mmol) was added dropwise to a stirred solution of L-*tert*-leucine (300 mg, 2.29 mmol) and di-*tert*-butyl dicarbonate (599 mg, 2.74 mmol) in dioxane/ water 1:1 (8 mL) and the solution was stirred overnight. The mixture was extracted with petroleum ether (2x) and the aqueous phase was cooled to 0 °C and carefully acidified to pH 3 by slow addition of 4M $NaHSO_4 \cdot H_2O$. The acidified water phase was extracted with EtOAc (3x) and the combined organic phases were washed with brine (2x) and was then dried, filtered and concentrated to give

compound 36 (522 mg, 99 %) as a colorless powder. No further purification was needed.

^{1}H-NMR (300 MHz, CD_3OD) δ 0.99 (s, 9H), 1.44 (s, 9H), 3.96 (s, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD) δ 27.1, 28.7, 34.9, 68.0, 80.5, 157.8, 174.7.

Example 37

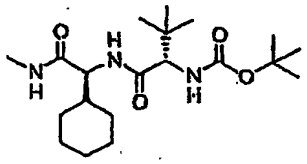


((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamic acid *tert*-butyl ester (37).

Boc-Chg-OH (387 mg, 1.50 mmol) was coupled to methylamine hydrochloride (111 mg, 1.65 mmol) using the same HATU coupling conditions as in the synthesis of compound 34. The crude product was extracted with EtOAc, washed with brine and concentrated. Purification by flash column chromatography (EtOAc) provided compound 37 (307 mg, 76 %) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91-1.13 (m, 2H), 1.14-1.31 (m, 3H), 1.44 (s, 9H), 1.61-1.80 (m, 6H), 2.80 (d, J = 4.7 Hz, 3H), 3.91 (dd, J = 7.1, 9.1 Hz, 1H), 5.23 (b, 1H), 6.52 (bs, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 25.9, 26.0, 26.1, 28.3, 28.5, 29.6, 40.5, 59.5, 79.7, 155.9, 172.4.

Example 38

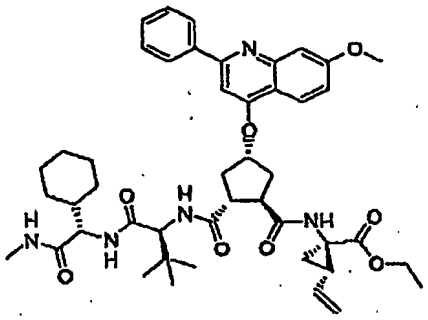


{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (38)

To a solution of compound 37 (98 mg, 0.362 mmol) in methylene chloride (3 mL) were added triethylsilane (115 mL, 0.742 mmol) and TFA (3 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene. The deprotected amine was dissolved in DMF (5 mL) and coupled to compound 36 (84 mg, 0.363 mmol) using the same HATU coupling conditions as in the synthesis of 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification by flash column chromatography (toluene/ EtOAc 1:1) provided compound 38 (128 mg, 92 %) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.02-1.30 (m, 5H), 1.44 (s, 9H), 1.58-1.77 (m, 4H), 1.78-1.89 (m, 2H), 2.79 (d, J = 4.7 Hz, 3H), 4.11 (d, J = 9.3 Hz, 1H), 4.33 (app. t, J = 8.5 Hz, 1H), 5.65 (b, 1H), 7.25 (b, 1H), 7.39 (b, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 25.9, 25.9, 26.0, 26.2, 26.8, 28.4, 29.0, 29.7, 34.5, 39.7, 58.4, 62.4, 79.4, 156.0, 171.4, 171.8.

Example 39



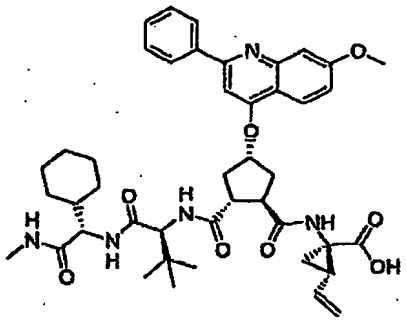
(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (39)

To a solution of compound 35 (30 mg, 0.060 mmol) in methylene chloride (1.5 mL) were added triethylsilane (21 µL, 0.132 mmol) and TFA (1.5 mL). The mixture was stirred for 2 h at room temperature and was then evaporated and coevaporated with toluene. The amine 38 (1.3 eq) was deprotected in the same manner as compound 35 and was then coupled to deprotected compound 35 using the same HATU coupling conditions as in the synthesis of 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification using HPLC (MeOH/ water 9:1 + 0.2% triethylamine) provided compound 39 (30 mg, 74%) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ 0.81-1.14 (m, 4H), 0.99 (s, overlapped, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.35-1.51 (m, 4H), 1.52-1.65 (m, 3H), 1.66-1.72 (m, 2H), 2.03-2.20 (m, 2H), 2.24-2.39 (m, 1H), 2.46-2.56 (m, 1H), 2.66 (s, 3H), 2.72-2.85 (m, 1H), 3.39-3.48 (m, 2H), 3.90 (s, 3H), 4.03-4.15 (m, 3H), 4.44 (s, 1H), 5.09 (dd, *J* = 1.9, 10.3 Hz, 1H), 5.19-5.27 (m, 1H), 5.25 (dd, overlapped, 1H), 5.79 (ddd, *J* = 8.8, 10.3, 17.2 Hz, 1H), 6.99 (s, 1H), 7.07 (dd, *J* = 2.5, 9.1, Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.43-7.52 (m, 3H), 7.86-7.98 (m, 2H), 8.05 (d, *J* = 9.3 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD) δ 14.7, 23.4, 26.0, 26.9, 27.1, 27.3, 30.1, 30.7, 35.0, 35.4, 38.3, 38.8, 40.9, 41.0, 47.9, 55.9, 59.6, 62.0, 62.4, 79.8, 99.9, 107.3, 116.4, 118.0, 119.1, 124.4, 128.9, 129.8, 130.5, 135.3, 141.3, 152.1, 161.1, 162.4, 163.0, 171.6, 172.5, 173.7, 175.2, 176.8.

Maldi-TOF-spectrum: $(M+H)^+$ calcd: 810.4, found: 810.5; $(M+Na)^+$ calcd: 832.4, found: 832.4; $(M+K)^+$ calcd: 848.5, found: 848.4.

Example 40



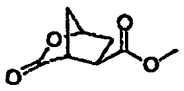
(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (40)

To a solution of compound 39 (20 mg, 0.025 mmol) in THF/MeOH/water 2:1:1 (2 mL) at 0 °C was added 1M LiOH (175 µL, 0.175 mmol) and the solution was allowed to attain room temperature and was stirred for 48 h. The solution was acidified to pH 3 with 1M HCl and was then evaporated and coevaporated with toluene. The crude product was purified by HPLC (MeOH/ water 6:4 + 0.5% TFA followed by MeOH/ water 4:1 + 0.2% TFA) to give compound 40 (13 mg, 67 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ 0.82-0.98 (m, 1H), 1.01 (s, 9H), 1.05-1.26 (m, 3H), 1.34-1.43 (m, 1H), 1.49-1.77 (m, 8H), 2.10-2.21 (m, 1H), 2.28-2.42 (m, 2H), 2.50-2.61 (m, 1H), 2.64 (s, 3H), 2.68-2.81 (m, 1H), 3.36-3.45 (m, 2H), 4.04-4.11 (m, 1H), 4.06 (s, overlapped, 3H), 4.27 (d, J = 8.8 Hz, 1H), 5.10 (dd, J = 1.8, 10.3 Hz, 1H), 5.28 (dd, J = 1.8, 17.2 Hz, 1H), 5.59-5.68 (m, 1H), 5.82 (ddd, J = 9.1, 10.3, 17.2 Hz, 1H), 7.44 (dd, J = 2.5, 11.8 Hz, 1H), 7.50 (s, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.69-7.78 (m, 3H), 8.02-8.07 (m, 2H), 8.39 (d, J = 9.3 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD) δ 23.5, 26.0, 26.9, 27.2, 27.3, 30.0, 30.7, 34.7, 35.3, 37.0, 38.7, 41.0, 41.3, 47.4, 56.9, 59.4, 62.7, 83.9, 100.4, 102.2, 116.2, 117.7, 121.7, 126.7, 129.8, 130.8, 133.4, 133.9, 135.6, 143.5, 158.0, 166.6, 168.6, 172.5, 173.4, 173.6, 175.4, 176.4. Maldi-

TOF-spectrum: $(M+H)^+$ calcd: 782.4, found: 782.2; $(M+Na)^+$ calcd: 804.4, found: 804.2; $(M+K)^+$ calcd: 820.5, found: 820.2.

Example 41

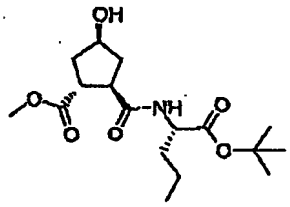


3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid methyl ester (41)

Compound 32 (1.014 g, 6.50 mmol) was dissolved in acetone (35 mL) before methyl iodide (13.68 g, 96.4 mmol) and silver(I)oxide (1.61 g, 6.95 mmol) were added. After stirring for 3h the mixture was filtered through celite and the filtrate was evaporated before purification by flash column chromatography (toluene/ethyl acetate 4:1) was performed yielding the methyl ester 41 (702 mg, 64 %) as white crystals.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.96 (d, J = 10.7 Hz, 1H), 2.21-2.25 (m, 3H), 2.91-2.95 (m, 1H), 3.16 (s, 1H), 3.75 (s, 3H), 4.98 (app. s, 1H).

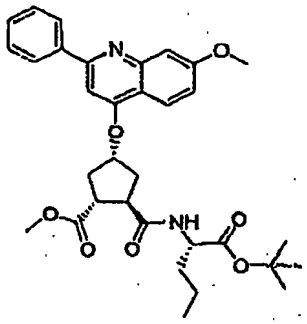
Example 42



(1*R*,2*R*,4*S*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-hydroxy-cyclopentanecarboxylic acid methyl ester (42)

Compound 41 (263 mg, 1.55 mmol) and H-Nva-O*t*Bu (420 mg, 2.42 mmol) were dissolved in dry THF (20 mL). DIEA (530 µL, 3.04 mmol) and 2-hydroxypyridine (260 mg, 2.73 mmol) were added and the mixture was refluxed for five days. The solvent was evaporated and the crude product was purified by flash column chromatography (toluene/ EtOAc 1:2) to give 42 (510 mg, 96%).

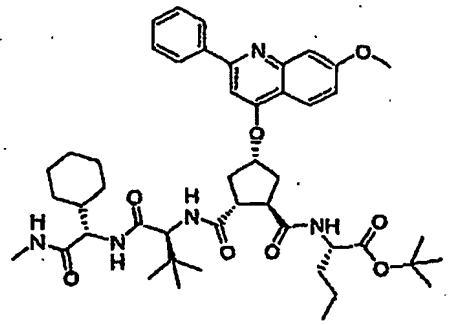
Example 43



(1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-Butoxycarbonyl-butylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester (43)

Compound 42 (249 mg, 0.725 mmol), 2-phenyl-7-methoxy-4-quinolinol (310 mg, 1.23 mmol) and PPh_3 (580 mg, 2.21 mmol) were dissolved in dry THF and the temperature was lowered to 0°C. DIAD (435 µL, 2.21 mmol) dissolved in 2 mL dry THF, was added to the mixture during five minutes. After two hours the temperature was raised to room temperature and the solution was stirred overnight. Evaporation and purification by flash column chromatography (toluene/ EtOAc gradient 6:1 to 4:1) gave 43 (324 mg, 78%).

Example 44

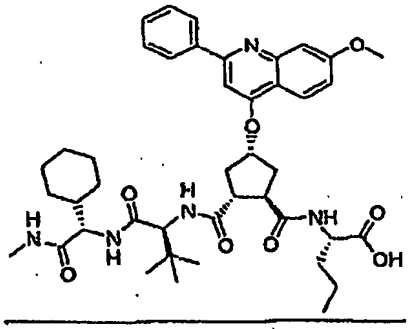


(*S*)-2-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid *tert*-butyl ester (44)

Compound 43 (38 mg, 0.066 mmol) was dissolved in dioxane/ water 1:1 (4 mL) and the solution was cooled to 0 °C and 1 M LiOH (132 µl, 0.132 mmol) was added. The temperature was raised to room temperature and the solution was stirred for 2 hours after which it was neutralized by addition of 1M HCl and evaporated and coevaporated with toluene. The residue and deprotected amine 38 (1.1 eq) was dissolved in DMF and coupled using the standard HATU coupling conditions as in the synthesis of compound 34. The crude product was extracted with EtOAc, washed with brine, dried, filtered and concentrated. Purification with HPLC (MeOH/ water 9:1 + 0.2% TEA) provided compound 44 (44 mg, 81 %) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) rotamers (5:1) δ 0.79 (t, J = 7.3 Hz, 3H), 0.85-1.19 (m, 3H), 0.93 (s, overlapped, 9H), 1.20-1.35 (m, 2H), 1.39 (s, 1.5 H), 1.43 (s, 7.5 H), 1.54-1.79 (m, 6H), 2.06-2.28 (m, 3H), 2.39-2.51 (m, 2H), 2.66-2.78 (m, 1H), 2.74 (d, overlapped, J = 4.7 Hz, 3H), 3.42-3.68 (m, 2H), 3.84 (s, 2.5 H), 3.88 (s, 0.5 H), 4.19 (t, J = 8.9 Hz, 1H), 4.39-4.59 (m, 1H), 4.68 (d, J = 9.6 Hz, 1H), 5.04-5.14 (m, 1H), 6.77 (s, 1H), 6.88-7.06 (m, 2H), 7.26-7.47 (m, 6H), 7.53 (b, 1H), 7.85-7.97 (m, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 13.7, 18.7, 25.6, 25.7, 26.0, 26.7, 28.0, 28.9, 29,7, 34.5, 34.7, 37.7, 38.0, 39.2, 46.6, 47.7, 52.7, 55.3, 58.5, 60.3, 77.9, 81.7, 98.0, 107.4, 115.0, 117.9, 122.8, 127.4, 128.6, 129.0, 140.2, 151.2, 158.9, 160.6, 161.1, 170.9, 171.6, 171.8, 172.7, 173.3. Maldi-TOF-spectrum: $(M+H)^+$ calcd: 828.5, found: 828.6; $(M+Na)^+$ calcd: 850.6, found: 850.6; $(M+K)^+$ calcd: 866.6, found: 866.6.

Example 45



(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (45)

Compound 44 (21 mg, 0,025 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and triethylsilane (10 µL, 0.063 mmol) and TFA (1.5 mL) were added. The solution was stirred for 2 hours at room temperature after which the solvents were evaporated and coevaporated with toluene to provide compound 45 (20 mg, 100 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ 0.93 (t, overlapped, 3H), 0.98 (s, 9H), 0.99-1.25 (m, 4H), 1.30-1.49 (m, 3H), 1.50-1.90 (m, 8H), 2.25-2.39 (m, 2H), 2.54-2.62 (m, 1H), 2.64 (s, 3H), 2.72-2.87 (m, 1H), 3.34-3.57 (m, 3H), 4.02-4.13 (m, 1H), 4.06 (s, overlapped, 3H), 4.27-4.36 (m, 1H), 4.37-4.47 (m, 1H), 5.57-5.66 (m, 1H), 7.45 (dd, *J* = 2.3, 9.2 Hz, 1H), 7.48 (s, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.69-7.79 (m, 3H), 8.01-8.07 (m, 2H), 8.42 (d, *J* = 9.3 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD) δ 14.0, 20.2, 26.0, 26.9, 27.2, 30.1, 30.7, 34.6, 35.3, 37.2, 39.1, 41.2, 47.7, 53.7, 56.9, 59.4, 59.5, 62.5, 83.7, 100.4, 101.3, 102.2, 116.2, 121.7, 126.7, 129.8, 130.8, 133.3, 133.9, 143.5, 157.9, 166.6, 168.5, 172.5, 173.6, 175.3, 175.4, 175.5.

Maldi-TOF-spectrum: $(M+H)^+$ calcd: 772.4, found: 772.6; $(M+Na)^+$ calcd: 794.4, found: 794.6; $(M+K)^+$ calcd: 810.5, found: 810.6.

Example 46

Hept-6-enal (46)

To a solution of hept-6-en-1-ol (1 mL, 7.44 mmol) and N-methylmorpholine N-oxide (1.308 g, 11.17 mmol) in DCM (17 mL) was added ground molecular sieves (3.6 g, 4 Å). The mixture was stirred for 10 min at room temperature under nitrogen atmosphere before tetrapropylammonium perruthenate (TPAP) (131 mg, 0.37 mmol) was added. After stirring for additional 2.5 h the solution was filtered through celite. The solvent was then carefully evaporated and the remaining liquid was purified by flash column chromatography (DCM) to give the volatile aldehyde 46 (620 mg, 74%) as an oil.

Example 47

N'-Hept-6-en-(*E*)-ylidene-hydrazinecarboxylic acid *tert*-butyl ester (47)

To a solution of 46 (68 mg, 0.610 mmol) and *tert*-butyl carbazate (81 mg, 0.613 mmol) in MeOH (5 mL) was added ground molecular sieves (115 mg, 3Å). The mixture was stirred for 3 h after which it was filtered through celite and evaporated. The residue was dissolved in dry THF (3 mL) and AcOH (3mL). $NaBH_3CN$ (95 mg, 1.51 mmol) was added and the solution was stirred over night. The reaction mixture was diluted with saturated $NaHCO_3$ solution (6 mL) and EtOAc (6 mL). The organic phase was washed with brine, saturated $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated. The cyanoborane adduct was hydrolyzed by treatment with MeOH (3 mL) and 2 M NaOH (1.9 mL). The mixture was stirred for 2 h and the MeOH was evaporated. H_2O (5 mL) and DCM (5 mL) were added and the water phase was extracted three times with DCM. The combined organic phases were dried and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 9:1 with 1 % triethylamine and toluene/ethyl acetate 6:1 with 1 % triethylamine) provided 47 (85 mg, 61 %) as an oil.

Example 48

(1*R*,2*S*)-1-{[(1*R*,2*R*,4*R*)-2-(*N'-tert*-Butoxycarbonyl-*N*-hept-6-enyl-hydrazinocarbonyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (48)

Scaffold molecule 35 (135 mg, 0.225 mmol) and triethylsilane (71 µL, 0.447 mmol) was dissolved in DCM (2 mL) after which trifluoroacetic acid (TFA) (2 mL) was added. The mixture was stirred for 2 h and thereafter co-evaporated with toluene in order to remove the TFA. The residue was dissolved in DMF (3 mL) and 47 (60 mg, 0.263 mmol) and DIEA (118 µL, 0.677 mmol) were added. The temperature was lowered to 0° C and the coupling reagent O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (94 mg, 0.247 mmol) was added. The cold solution was allowed to stir for half an hour and then for additional 16 h in room temperature. The solvent was removed by heating the reaction flask in a water bath under diminished pressure. The residue was thereafter dissolved in ethyl acetate and the organic phase was washed three times with brine, dried, filtered and evaporated. Purification by HPLC (MeOH/H_2O 90:10 with 0.2 % triethylamine) gave 48 (140 mg, 82 %) as an oil.

^{1}H-NMR (300 MHz, $CDCl_3$, 40° C): δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.28-1.42 (m, 6H), 1.46 (s, 9H), 1.52-1.62 (m, 2H), 1.82-1.91 (m, 1H), 1.96-2.16 (m, 3H), 2.18-2.34 (m, 2H), 2.42-2.56 (m, 1H), 2.58-2.72 (m, 1H), 3.42 (app. bs, 3H), 3.66-3.84 (m, 1H), 3.92 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.88-5.02 (m, 2H), 5.07-5.18 (m, 2H), 5.20-5.32 (m, 1H), 5.63-5.84 (m, 2H), 6.62 (bs, 1H), 6.94 (s, 1H), 7.09 (dd, *J* = 2.6, 9.2 Hz, 1H), 7.36-7.51 (m, 4H), 7.99-8.10 (m, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.3, 23.0, 26.4, 26.6, 28.3, 28.6, 33.2, 33.5, 35.6, 37.6, 40.6, 44.7, 47.1, 48.6, 55.5, 61.5, 81.9, 98.4, 107.9, 114.5, 115.6, 118.1, 123.2, 127.6, 128.3, 128.7, 129.1, 133.5, 138.7, 140.7, 151.5, 154.5, 159.2, 160.9, 161.5, 170.5, 174.2, 176.3.

Example 49

(*Z*)-(1*R*,4*R*,6*S*,16*R*,18*R*)-14-*tert*-Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid ethyl ester (49)

A solution of 48 (158 mg, 0.209 mmol) in dry DCM (25 mL) was bubbled with argon for 5 min. To the stirred solution under argon atmosphere was then added a solution of Hoveyda-Grubbs catalyst 2nd generation (11 mg, 0.018 mmol) in dry DCM (5 mL). The mixture was stirred at reflux under argon atmosphere for 16 h. The solvent was evaporated and purification by HPLC (MeOH/H_2O 90:10 with 0.2 % triethylamine) yielded 49 (107 mg, 70 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ 1.03-1.22 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.32-1.44 (m, 4H), 1.49 (s, 9H), 1.55-1.73 (m, 2H), 1.81-1.91 (m, 1H), 2.04-2.28 (m, 3H), 2.30-2.52 (m, 3H), 2.53-2.70 (m, 1H), 2.86-3.00 (m, 1H), 3.34-3.44 (m, 1H), 3.46-3.62 (m, 1H), 3.95 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.32-4.48 (m, 1H), 5.20-5.33 (m, 1H), 5.34 (bs, 1H), 5.58-5.70 (m, 1H), 7.10 (s, 1H), 7.14 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.45-7.55 (m, 3H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 9.3 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 14.6, 23.4, 27.5, 27.7, 28.0, 28.5, 30.7, 36.1, 38.1, 42.5, 45.6, 56.0, 62.7, 79.9, 82.8, 100.2, 107.4, 116.6, 119.1, 124.5, 126.5, 128.9, 129.8, 130.5, 135.8, 141.6, 152.2, 156.4, 161.3, 162.5, 163.1, 171.9, 175.8, 179.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 727.4, found: 727.5.

Example 50

(*Z*)-(1*R*,4*R*,6*S*,16*R*,18*R*)-14-*tert*-Butoxycarbonylamino-18-(7-methoxy-2-phenyl-quinolin-4-yloxy)-2,15-dioxo-3,14-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (50)

To a solution of 49 (27 mg, 0.037 mmol) in THF/MeOH/H_2O 2:1:1 (5 mL) was added 1 M LiOH (300 µL, 0.300 mmol). The solution was stirred for 24 h at room temperature and finally for one hour at reflux. After acidification to pH 3-4 with 1 M

HCl and evaporation the residue was purified by HPLC (MeOH/H_2O 80:20 and MeOH/H_2O 90:10) providing 50 (12 mg, 46 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ 1.06-1.24 (m, 1H), 1.26-1.42 (m, 3H), 1.48 (s, 9H), 1.62-1.73 (m, 3H), 1.80-1.90 (m, 1H), 2.02-2.15 (m, 1H), 2.15-2.40 (m, 4H), 2.43-2.54 (m, 1H), 2.54-2.68 (m, 1H), 2.88-3.00 (m, 1H), 3.35-3.48 (m, 1H), 3.49-3.66 (m, 1H), 3.96 (s, 3H), 4.32-4.48 (m, 1H), 5.25-5.42 (m, 2H), 5.56-5.68 (m, 1H), 7.14 (s, 1H), 7.17 (dd, J = 2.5, 9.1 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.46-7.58 (m, 3H), 8.00 (d, J = 8.0 Hz, 2H), 8.19 (d, J = 9.1 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 23.6, 26.8, 27.8, 28.3, 28.5, 30.5, 35.8, 38.1, 43.0, 45.5, 56.0, 80.2, 82.7, 100.4, 106.9, 116.6, 119.2, 124.7, 127.4, 129.0, 129.8, 130.7, 134.8, 140.9, 151.6, 156.5, 161.1, 163.0, 163.4, 173.8, 175.7, 179.3.

Example 51

((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester (51).

To a cold solution of 36 (133 mg, 0.575 mmol), cyclopentylamine (64 µL, 0.648 mmol) and DIEA (301 µL, 1.73 mmol) in DMF (3 mL) was added the coupling reagent HATU (240 mg, 0.631 mmol). The mixture was stirred for half an hour and for additional two hours at room temperature. The solvent was removed by heating the reaction flask in a water bath under diminished pressure and the residue was dissolved in ethyl acetate, after which the organic phase was washed three times with brine, dried, filtered and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 4:1) provided 51 (140 mg, 82 %) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 1.28-1.48 (m, overlapped, 2H), 1.40 (s, 9H), 1.49-1.71 (m, 4H), 1.86-2.01 (m, 2H), 3.76 (b, 1H), 4.09-4.23 (m, 1H), 5.32 (b, 1H), 5.91 (b, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 23.6, 23.7, 26.5, 28.3, 32.6, 33.1, 34.5, 51.0, 62.2, 79.4, 155.9, 170.3.

Example 52

(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (52)

Compound 51 (298 mg, 0.048 mmol) and 35 (16 mg, 0.054 mmol) was deprotected and coupled according to the method for the preparation of 39. Purification by HPLC ($MeOH/H_2O$ 90:10 with 0.2 % triethylamine) gave 52 (22 mg, 63 %) as a colorless solid.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.97 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.26-1.37 (m, 1H), 1.38-1.46 (m, 2H), 1.48-1.58 (m, 4H), 1.78-1.85 (m, 1H), 1.86-2.02 (m, 3H), 2.03-2.19 (m, 1H), 2.28-2.40 (m, 2H), 2.41-2.54 (m, 1H), 2.64-2.78 (m, 1H), 3.10-3.24 (m, 1H), 3.30-3.44 (m, 1H), 3.95 (s, 3H), 4.04-4.21 (m, 3H), 5.12 (dd, *J* = 1.7, 10.3 Hz, 1H), 5.14-5.22 (m, 1H), 5.28 (dd, *J* = 1.7, 17.0 Hz, 1H), 5.59 (b, 1H), 5.75 (ddd, *J* = 8.8, 10.3, 17.0 Hz, 1H), 6.66-6.82 (m, 2H), 6.99 (s, 1H), 7.09 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.41-7.55 (m, 4H), 7.99-8.09 (m, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.3, 22.9, 23.6, 23.6, 26.7, 32.7, 33.2, 33.7, 34.8, 35.9, 36.6, 40.2, 46.4, 47.5, 51.3, 55.5, 61.1, 61.4, 78.0, 98.4, 107.1, 115.2, 117.9, 118.2, 123.1, 127.6, 128.8, 129.3, 133.5, 159.1, 161.4, 169.4, 169.9, 173.1, 174.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 725.4, found: 725.6; $(M+Na)^+$ calcd: 747.4, found: 747.6; $(M+K)^+$ calcd: 763.3, found: 763.5.

Example 53

(1*R*,2*S*)-1-{[(1*R*,2*R*,4*S*)-2-((*S*)-1-Cyclopentylcarbamoyl-2,2-dimethyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (53).

To a solution of 52 (14 mg, 0.019 mmol) in dioxane/H_2O 1:1: (4 mL) was added 1 M LiOH (115 µL, 0.115 mmol). The solution was stirred for 24 h at room temperature. Thereafter an additional portion of LiOH (75 µL, 0.075 mmol) was added and the

solution was stirred for another 24 h. After acidification to approximately pH 3 with 1 M HCl and co-evaporation with toluene the residue was purified by HPLC (MeOH/H_2O 70:30 with 0.2 % TFA) yielding 53 (8 mg, 60 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.98 (s, 9H), 1.28-1.48 (m, 3H), 1.49-1.76 (m, 5H), 1.78-1.94 (m, 2H), 2.10-2.24 (m, 1H), 2.26-2.45 (m, 2H), 2.50-2.62 (m, 1H), 2.66-2.79 (m, 1H), 3.35-3.48 (m, 2H), 3.94-4.03 (m, 1H), 4.06 (s, 3H), 4.16-4.24 (m, 1H), 5.10 (dd, J = 1.8, 10.3 Hz, 1H), 5.29 (dd, J = 1.8, 17.2 Hz, 1H), 5.62 (b, 1H), 5.82 (ddd, J = 9.1, 10.3, 17.2 Hz, 1H), 7.43 (dd, J = 2.5, 9.3 Hz, 1H), 7.50 (s, 1H), 7.50-7.69 (dd, overlapped, 1H), 7.67-7.80 (m, 3H), 8.01-8.11 (m, 2H), 8.39 (d, J = 9.3 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 24.7, 24.7, 27.3, 33.1, 33.6, 34.7, 35.4, 36.9, 38.7, 41.0, 47.4, 52.3, 56.9, 62.3, 83.9, 100.4, 102.3, 116.2, 117.7, 121.6, 126.7, 129.8, 130.8, 133.4, 133.8, 135.6, 143.5, 158.0, 166.5, 168.6, 171.9, 173.4, 175.2, 176.4. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 697.4, found: 697.3; $(M+Na)^+$ calcd: 718.7, found: 719.3; $(M+K)^+$ calcd: 735.3, found: 735.3.

Example 54
(*S*)-*tert*-Butoxycarbonylamino-cyclohexyl-acetic acid methyl ester (54).

To a solution of Boc-Chg-OH (53 mg, 0.206 mmol) in acetone (3 mL) were added methyl iodide (195 µL, 3.1 mmol) and silver (I) oxide (53 mg, 0.229 mmol). The mixture was allowed to stir over night in a reaction flask that was covered with aluminium foil. Thereafter the solution was filtered through celite and evaporated. Purification by flash column chromatography (toluene/ethyl acetate 15:1) provided methyl ester 54 (56 mg, 100 %) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.00-1.34 (m, 5H), 1.44 (s, 9H), 1.54-1.82 (m, 6H), 3.73 (s, 3H), 4.20 (dd, J = 2.8, 5.0 Hz, 1H), 5.05 (bs, 1H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 26.0, 28.2, 28.3, 29.5, 41.1, 52.0, 58.3, 79.7, 155.6, 172.9.

Example 55

(*S*)-((*S*)-2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (55)

Compound 54 (93 mg, 0.343 mmol) was deprotected and coupled to Z-Val-OH (95 mg, 0.378 mmol) according to the method for the preparation of 39. Flash column chromatography (toluene/ethyl acetate 4:1) gave 55 (131 mg, 94 %) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.92-1.30 (m, 11H), 1.54-1.88 (m, 6H), 2.02-2.18 (m, 1H), 3.72 (s, 3H), 4.05-4.18 (m, 1H), 4.52 (dd, *J* = 3.0, 5.5 Hz, 1H), 5.12 (s, 2H), 5.49 (bs, 1H), 6.52 (bs, 1H), 7.34 (s, 5H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 17.8, 19.0, 25.8, 28.2, 29.3, 31.2, 40.5, 51.9, 56.8, 60.0, 66.8, 127.7, 127.9, 128.1, 128.3, 136.2, 156.3, 171.3, 172.2.

Example 56

(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino)-pentanoic acid *tert*-butyl ester (56).

To a solution of 55 (40 mg, 0.099 mmol) in ethanol (95%) (7.5 mL) was added palladium on active carbon (10 %, 40 mg) and the mixture was hydrogenated under pressure at room temperature for 2 h. The mixture was filtered through celite and evaporated. Compound 43 (38 mg, 0.083 mmol) was dissolved in dioxane/H_2O 1:1 (3 mL) and the mixture was cooled to 0° C before 1 M LiOH (140 µL, 0.140 mmol) was added to the stirred solution. After 1h the mixture was neutralized with 1 M hydrochloric acid and the solvent was evaporated and co-evaporated with toluene. The residue was coupled to deprotected 55 using the same HATU coupling conditions as in the synthesis of compound 48. Purification by HPLC (MeOH/H_2O 90:10 with 0.2 % triethylamine) gave 56 (56 mg, 88 %) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82-0.96 (m, 9H), 0.82-1.22 (m, overlapped, 6H), 1.23-1.40 (m, 2H), 1.44 (s, 9H), 1.50-1.69 (m, 4H), 1.71-1.87 (m, 2H), 1.95-2.06 (m, 1H), 2.07-2.22 (m, 1H), 2.28-2.54 (m, 3H), 2.60-2.75 (m, 1H), 3.08-3.28 (m, 1H), 3.30-3.49 (m, 1H), 3.70 (s, 3H), 3.94 (s, 3H), 4.28-4.38 (m, 1H), 4.41-4.57 (m, 2H), 5.17 (b, 1H), 6.64-6.70 (m, 2H), 6.74 (b, 1H), 6.95 (s, 1H), 7.09 (dd, *J* = 2.5, 9.1 Hz, 1H), 7.39-7.55 (m, 5H), 7.98-8.10 (m, 3H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 13.7, 18.1, 18.6, 19.2, 25.9, 28.0, 28.2, 29.6, 30.7, 34.6, 36.5, 37.6, 40.8, 47.4, 47.5, 52.1, 52.8, 55.5, 56.8, 58.9, 77.8, 82.0, 98.3, 107.5, 115.3, 118.1, 123.1, 127.5, 128.7, 129.1, 140.5, 151.4, 159.2, 160.7, 161.3, 171.0, 171.5, 172.3, 172.8, 173.0. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 815.5, found: 815.7; $(M+Na)^+$ calcd: 837.4, found: 837.6; $(M+K)^+$ calcd: 853.4, found: 853.6.

Example 57

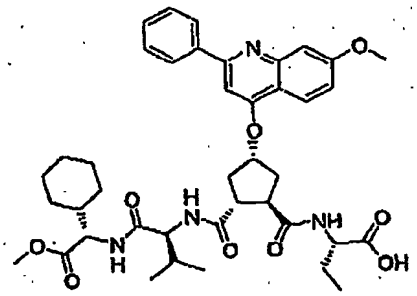
(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-pentanoic acid (57)

*Tert.*butyl ester 56 (28 mg, 0.034 mmol) and triethylsilane (14 µL, 0.088 mmol) was dissolved in DCM (2 mL) after which trifluoroacetic acid (2 mL) was added and the mixture was stirred for 2 h. Co-evaporation with toluene gave 57 (26 mg, 100 %) as a colorless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.86-1.00 (m, 9H), 1.01-1.24 (m, 4H), 1.36-1.46 (m, 2H), 1.48-1.75 (m, 8H), 1.70-1.89 (m, overlapped, 1H), 1.96-2.12 (m, 1H), 2.22-2.40 (m, overlapped, 2H), 2.49-2.64 (m, 1H), 2.72-2.91 (m, 1H), 3.26-3.40 (m, overlapped, 1H), 3.50-3.68 (m, overlapped, 1H), 3.62 (s, 3H), 4.05 (s, 3H), 4.09-4.17 (m, 1H), 4.17-4.25 (m, 1H), 4.35-4.45 (m, 1H), 5.62 (b, 1H), 7.44 (dd, *J* = 2.2, 9.3 Hz, 1H), 7.49 (s, 1H), 7.53 (d, *J* = 2.2 Hz, 1H), 7.65-7.78 (m, 3H), 7.98-8.06 (m, 2H), 8.41 (dd, *J* = 2.8, 9.3 Hz, 1H); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 13.9, 18.8, 19.7, 20.2, 27.0, 29.7, 30.5, 31.8, 34.6, 37.7, 38.9, 41.1, 47.8, 52.3, 53.6, 56.9, 58.8, 58.9, 60.3, 83.8, 100.4, 102.2, 116.2, 121.6, 126.7, 129.8, 130.8, 133.3, 133.8, 143.5, 157.9,

166.5, 168.5, 173.3, 173.9, 175.5, 175.5, 175.6. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 759.4, found: 759.7; $(M+Na)^+$ calcd: 781.4, found: 781.7; $(M+K)^+$ calcd: 797.4, found: 797.7.

Example 58



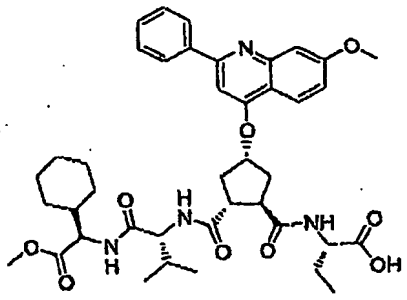
(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*S*)-1-[((*S*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (58).

The procedure described in example 42 was followed but with the use of L-2-amino-N-butyric acid tert.butyl ester instead of H-Nva-O*t*Bu. The afforded compound was then reacted as described in example 43 which gave (1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-butoxycarbonyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester. Coupling of this compound with 55 as described in example 56 followed by esterhydrolysis as described in example 57 gave 58 as a colourless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ 0.82-0.99 (m, 9H), 0.82-1.40 (m, overlapped, 6H), 1.48-1.78 (m, 6H), 1.80-1.95 (m, 1H), 1.97-2.12 (m, 1H), 2.22-2.40 (m, overlapped, 2H), 2.51-2.64 (m, 1H), 2.71-2.90 (m, 1H), 3.16-3.39 (m, overlapped, 1H), 3.49-3.59 (m, 1H), 3.63 (s, 3H), 3.95 (s, 3H), 4.12-4.23 (m, 2H), 4.28-4.38 (m, 1H), 5.31 (b, 1H), 7.43 (dd, J = 2.2, 9.3 Hz, 1H), 7.47 (s, 1H), 7.51 (s, 1H), 7.66-7.89 (m, 3H), 7.99-8.07 (m, 2H), 8.42 (d, J = 9.1 Hz, 1H); ^{13}C-NMR (75.5 MHz, CD_3OD): δ 10.7, 18.8, 19.7, 25.8, 27.0, 27.0, 29.7, 30.5, 31.8, 37.7, 38.9, 41.2, 47.9, 52.3, 55.3, 56.9,

58.8, 60.6, 83.6, 100.7, 102.2, 116.3, 121.5, 126.7, 129.8, 130.8, 133.7, 133.8, 143.9, 158.2, 166.4, 168.3, 173.3, 173.8, 175.2, 175.5, 175.6. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 745.4, found: 744.9; $(M+Na)^+$ calcd: 767.4, found: 766.9; $(M+K)^+$ calcd: 783.5, found: 782.9.

Example 59



(*S*)-2-{[(1*R*,2*R*,4*S*)-2-{(*R*)-1-[((*R*)-Cyclohexyl-methoxycarbonyl-methyl)-carbamoyl]-2-methyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarbonyl]-amino}-butyric acid (59)

The procedure described in example 54 was followed but with the use of Boc-D-cyclohexylglycine instead of Boc-L-cyclohexylglycine. The afforded compound was then reacted as described in example 55 followed by coupling with (1*R*,2*R*,4*R*)-2-((*S*)-1-*tert*-Butoxycarbonyl-pentylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-cyclopentanecarboxylic acid methyl ester as described in example 56. Removal of the ester group as described in example 57 gave compound 59 as a colourless solid.

^{1}H-NMR (CD_3OD, 300 MHz): δ 0.82-1.02 (m, 9H), 1.04-1.42 (m, 6H), 1.52-1.80 (m, 6H), 1.80-1.96 (m, overlapped, 1H), 2.00-2.14 (m, 1H), 2.29-2.46 (m, 2H), 2.51-2.65 (m, 1H), 2.68-2.84 (m, 1H), 3.24-3.39 (m, overlapped, 1H), 3.47-3.60 (m, 1H), 3.67 (s, 3H), 4.07 (s, 3H), 4.18-4.27 (m, 2H), 4.28-4.38 (m, 1H), 5.64 (app. bs, 1H), 7.44 (d, J = 2.3, 6.9 Hz, 1H), 7.42 (s, 2H), 7.67-7.81 (m, 3H), 8.04 (d, J = 7.8 Hz, 2H), 8.41 (d, J = 9.1 Hz, 1H); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 10.8, 18.5, 19.6, 25.7,

27.1, 27.1, 30.1, 30.6, 31.9, 37.3, 38.2, 41.1, 47.8, 52.3, 55.4, 56.9, 59.0, 59.1, 60.2, 83.8, 100.5, 102.2, 116.3, 121.6, 126.8, 129.8, 130.8, 133.6, 133.8, 143.7, 158.1, 166.5, 168.5, 173.4, 173.8, 175.4, 175.7, 175.7. MALDI-TOF-spectrum: $(M+H)^+$ calcd: 745.4, found: 745.4; $(M+Na)^+$ calcd: 767.4, found: 767.4; $(M+K)^+$ calcd: 783.5, found: 783.3.

Example 60
N-Boc-4R-(2-phenyl-7-methoxyquinoline-4-oxo)proline (60).

To a stirred solution of N-Boc–trans-4-hydroxy-L-proline (3.9 g, 16.9 mmol) in DMSO (90mL) was added potassium tert.butoxide (4.5 g, 40.1 mmol). After 1 hrs 4-chloro-2-phenyl-7-methoxy quinoline (4.5g, 16.7 mmol) was added and stirred at RT for 12 hrs. The mixture was diluted with water (180 mL), washed with ethyl acetate (1x30mL) and neutralized with 1N HCl. The solid was filtered, washed with water and dried giving (4.65g, 10mmol) of product. >95% purity by HPLC. $M+H^+$ 464.2.

Example 61
2-(1-Ethoxycarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-2-phenyl-quinoline-4-yloxy)-pyrrolidine-1-carboxylic acid *tert*.butyl ester (61).

To a solution of 1-amino-2-vinyl-cyclopropanecarboxylic acid ethyl ester (41 mg, 0.26 mmol), 60 (11 mg, 0.22 mmol), HATU (204 mg, 0.54 mmol) in DMF (4 mL) was added diisopropyehtylamine (187 µL, 1.08 mmol). After stirring at RT for 1 hrs, dichloromethane (4 mL) was added. The solution was washed with aqueous $NaHCO_3$ (sat) and with two portions of water. The organic layer was dried and concentrated. The product was pure enough (>95 % by HPLC) to be used in the next step. $M+H^+$ 602.2.

Example 62
1-{[4-(7-Methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (62).

Compound 61 was kept in TFA-DCM 1:2 (3 mL) at RT for 60 min. Toluene (3 mL) was added. The sample was co-evaporated to dryness. Purity by HPLC >95%. $M+H^+$ 502.4.

Example 63

1-{[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid ethyl ester (63).

To a solution of compound 62 (0.13 mmol) in THF (2 mL), was added a large excess of $NaHCO_3$ (s) and a solution of phosgene in toluene (1.6 M, 600 µL). After 10 min of agitation the slurry was filtered and concentrated to dryness. The solid was redissolved in dichloromethane and a large excess of $NaHCO_3$ (s) and 2-Amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide (0.65 mmol) was added. The slurry was agitated for 24-40 hrs at RT. The slurry was filtered, concentrated and subjected to silica column chromatography (gradient elution from 100 % DCM to MeOH/DCM 2:98) to give the title compound (89.6 mg, 0.11 mmol). Purity by HPLC >95%. $M+H^+$ 790.3.

Example 64

1-[1-[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propyl]-4-(6-methoxy-3-phenyl-naphthalen-1-yloxy)-pyrrolidin-2-yl]-2-vinyl-cyclopropanecarboxylic acid (64).

To a solution of 63 (76.7mg, 0.097mmol) in THF-MeOH 2:3 (2 mL) was added 1M LIOH 5 equiv. The solution was kept at 60 °C for 60 min. After cooling to RT, HOAc 15-30 eq. was added followed by toluene (2 mL) and then concentrated to dryness. The residue was taken up in DCM and washed with water. The organic layer was dried and concentrated to give the title compound (72 mg, 0.094 mmol). Purity >95% by HPLC $M+H^+$ 762.2.

Example 65

N-(2-Hydroxy-indan-1-yl)-2-[4-(6-methoxy-3-phenyl-naphthalen-1-yloxy)-2-(1-phenylmethanesulfonylaminocarbonyl-2-vinyl-cyclopropyl)-pyrrolidin-1-yl]-3,3-dimethyl-butyramide (65).

To solution of 64 (25 mg, 0.033 mmol) in chloroform (1 mL) was added benzenesulfonamide (10.5 mg, 0.066 mmol) followed by diisopropylethylamine (34 µL, 0.197mmol). The solution was stirred at RT for 10 min and then at -20 °C for 30 min. PyBOP (76 mg, 0.13 mmol) was then added as a solid. The solution was kept at -20 °C for 48 hours. The solution was then poured into aqueous $NaHCO_3$ (sat.) and washed with water. The organic layer was dried, concentrated and subjected to purification by HPLC, affording the title compound as a white solid.

Example 66

Resin bound 2-tert.butoxycarbonylamino-3,3-dimetylbutyric acid (66).

To Argonaut resin PS-TFP (1.38 mmol/g, 10 g) and 2-*tert*-butoxycarbonylamino-3,3-dimethyl-butyric acid (4.5 g, 20.7mmol) was added dichloromethane (40 mL) and DMF (10 mL). To this mixture was added DMAP (1 g, 8.28 mmol) and then DIC (9.5 mL, 60.7 mmol). After 3 hrs of agitation at RT the resin was filtered and washed successively with DMF, THF, DCM, THF, DCM and ether and then dried in a vacuum.

Example 67

[1-(2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propyl]-carbamic acid *tert*.butyl ester (67).

To a portion of 66 (200 mg) in DCM aminoindanol (0.14 mmol) was added. The mixture was agitated for 2 hrs. The liquid was filtered of and the resin washed with 2xDCM. The combined liquids were combined and concentrated to dryness to afford the title compound (20.5 mg, 0.055 mmol) Purity >95% by HPLC. $M+H^+$ 363.15.

^{13}C NMR δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.0, 28.5, 34.2, 39. 8, 50.8, 57.9, 68.2, 73.7, 124.8, 125.6, 127.4, 128.5, 140.4, 171.6. ^1H NMR δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (9H, s, CCH_3), 1.44 (9H, s, $OCCH_3$), 2.93 (1H, dd, J_{gem}16.4 Hz, $J_{3,2}$ 2.3 Hz, CH_2), 3.15 (1H, dd, J_{gem}16.4 Hz, $J_{3,2}$ 5.2 Hz, CH_2),

Example 68

2-Amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl butyramide (68).

Compound 67 was kept in DCM-TFA 2:1 (2 mL) for 60 min at RT. The solution was co-evaporated with toluene to dryness.

Example 69

(2-*tert*-Butoxycarbonylamino-3,3-dimethyl-butyrylamino)-cyclohexyl-acetic acid methyl ester (69).

To a solution of 2-*tert*.butoxycarbonylamino-3,3-dimethyl butyric acid (500 mg, 2.16 mmol), Amino-cyclohexyl-acetic acid methyl ester (444 mg, 2.59 mmol) and HATU (2 g, 5.40 mmol) in DMF (20 mL) was added diisopropylethylamine (1.88 mL, 10.8 mmol). The solution was stirred for 1 hrs at r.t. and diluted with dichloromethane (40 mL). This solution was washed with aqueous. NaHCO3 (sat.) and water (x2), dried and concentrated. The product was >95 % pure. $M+H^+$ 385.4.

Example 70

{1-[(Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (70).

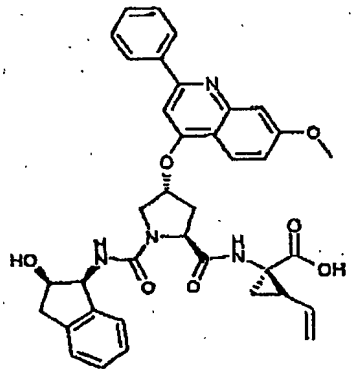
To compound 69 in EtOH-THF 1:2 was added a large excess of methylamine (30% in water) and left at rt. for 2 weeks. The solution was concentrated to dryness and the residue subjected to a short silica gel column eluted with 2% MeOH in dichloromethane to give a pure (>95%) product $M+H^+$ 384.5.

Example 71

2-Amino-*N*-(cyclohexyl-methylcarbamoyl-methyl)-3,3-dimethyl-butyramide (71).

Compound 70 was kept in dichloromethane-trifuoroacetic acid 2:1 for 1 h at rt and concentrated to dryness. The residue was dried in a vacuum for 16 hrs. Reversed phase C18 HPLC showed >95% purity M+H$^+$ 283.1.

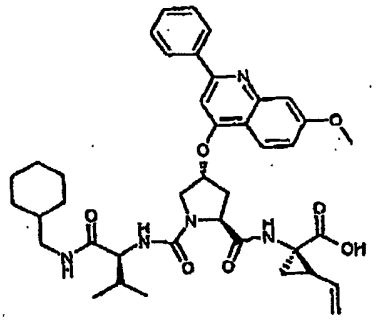
Example 72



(1R,2S)-1-{[(2S,4R)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarboxylic acid (72).

Compound 62 was treated as described for the preparation of 63 but with the use of (1S,2R)-cis-1-amino-2-indanol instead of 2-amino-N-(2-hydroxyindan-1-yl)-3,3-dimethyl butyramide followed by ester hydrolysis as described for the preparation of compound 64 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 649.1.

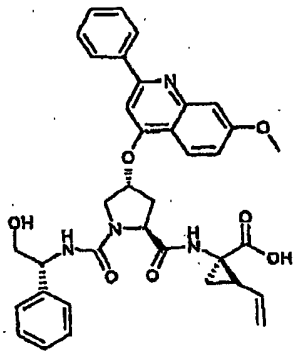
Example 73



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (73).

N-(tert-butoxycarbonyl)-L-valine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 712.3.

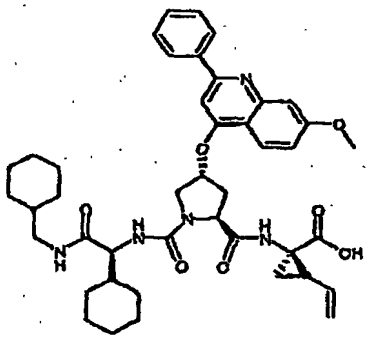
Example 74



(1R,2S)-1-{[(2S,4R)-1-((1R)-2-Hydroxy-1-phenyl-ethylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (74).

Compound 62 was treated as described for the preparation of 63 but with the use of (R)-2-phenylglycinol instead of 2-amino-N-(2-hydroxyindan-1-yl)-3,3-dimethyl butyramide instead of 2-amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide followed by ester hydrolysis as described for the preparation of compound 64 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 637.1.

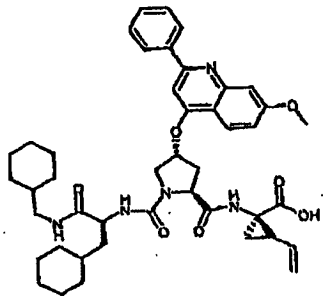
Example 75



(1R,2S)-1-{[(2S,4R)-1-{[(1S)-Cyclohexyl-(cyclohexylmethyl-carbamoyl)-methyl]-carbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (75).

N-(tert-butoxycarbonyl)-L-cyclohexylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 752.4.

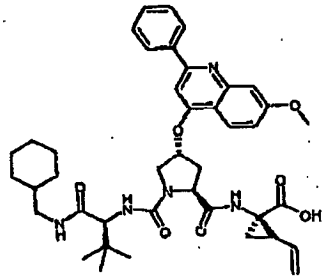
Example 76



(1R,2S)-1-{[(2S,4R)-1-[(1S)-2-Cyclohexyl-1-(cyclohexylmethyl-carbamoyl)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (76).

N-(tert-butoxycarbonyl)-L-cyclohexylalanine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 766.4.

Example 77

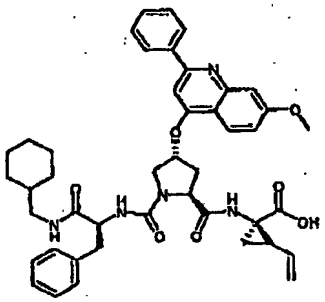


(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (77).

N-(tert-butoxycarbonyl)-L-tert-butylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for

68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 726.3.

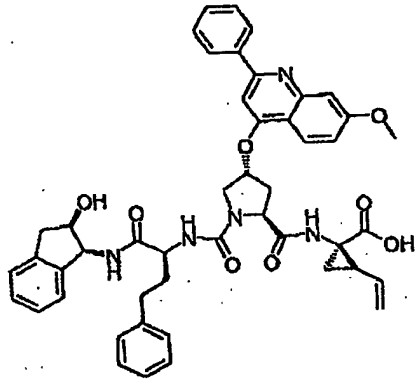
Example 78



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-(Cyclohexylmethyl-carbamoyl)-2-phenyl-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (78).

N-(tert-butoxycarbonyl)-L-phenylalanine was attached to the resin as described for the preparation of compound 66 followed by reaction with cyclohexanemethylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. M+H$^+$ 760.4.

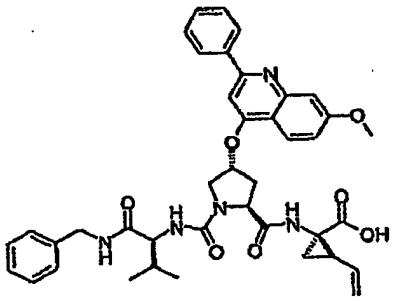
Example 79



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1S,2R)-2-Hydroxy-indan-1-ylcarbamoyl)-3-phenyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (79).

N-(tert.butoxycarbonyl)-L-phenethylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-cis-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 810.4.

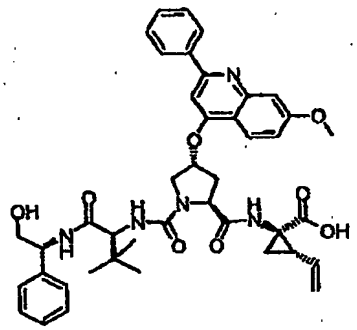
Example 80



(1R,2S)-1-{[(2S,4R)-1-((1S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (80).

N-(tert-butoxycarbonyl)-L-valine was attached to the resin as described for the preparation of compound 66 followed by reaction with benzylamine as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 706.2.

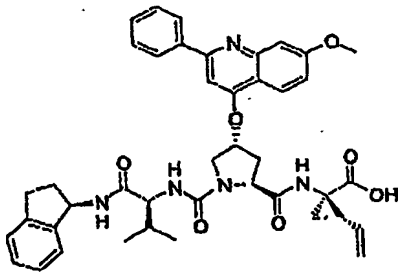
Example 81



(1R,2S)-1-{[(2S,4R)-1-[(1S)-1-((1R)-2-Hydroxy-1-phenyl-ethylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (81).

N-(tert-butoxycarbonyl)-L-tert-butylglycine was attached to the resin as described for the preparation of compound 66 followed by reaction with (R)-2-phenylglycinol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which gave the title compound. Purity by HPLC >95%. $M+H^+$ 750.3.

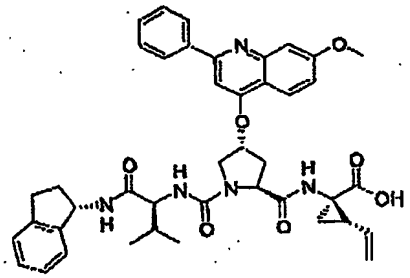
Example 82



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1R)-Indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (82).

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1R)-1-aminoindane as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12.5 mg, 28 % yield), Purity by HPLC >90%. $M+H^+$ 732.2.

Example 83

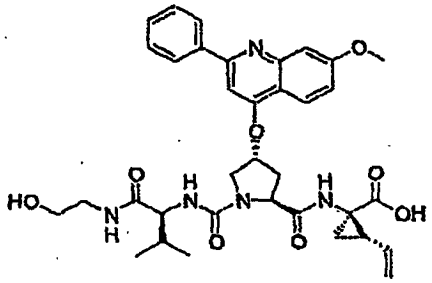


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S)-Indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (83).

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S)-1-

aminoindane as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (22 mg, 49 % yield), Purity by HPLC >90% $M+H^+$ 732.2.

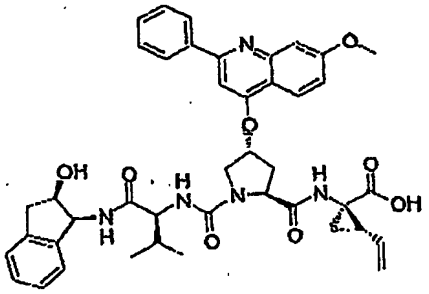
Example 84



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-(2-hydroxyethylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (84).

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with 2-aminoethanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (3 mg, 8 % yield), Purity by HPLC >90% $M+H^+$ 660.2.

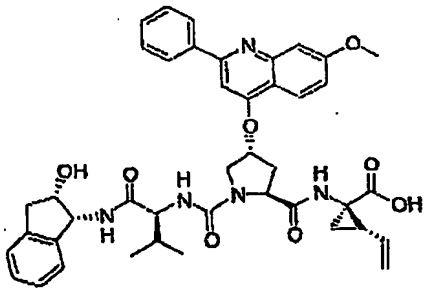
Example 85



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (85).

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (10 mg, 22 % yield), Purity by HPLC >90% $M+H^+$ 748.2.

Example 86

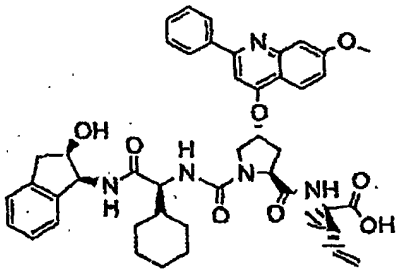


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1R, 2S)-2-Hydroxy-indan-1-ylcarbamoyl)-2-methyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (86).

(2S)-*tert*-butoxycarbonylamino-3-methylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1R,2S)-1-

amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (11 mg, 24 % yield), Purity by HPLC >75% $M+H^+$ 748.

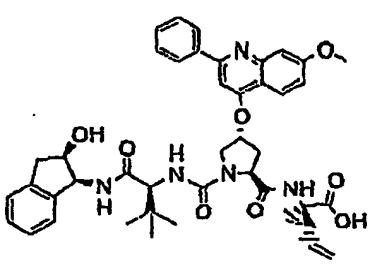
Example 87



(1R, 2S)-1-{[(2S, 4R)-1-{[Cyclohexyl-(S)-((1S, 2R)-2-hydroxy-indan-1-ylcarbamoyl)-methyl]-carbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (87).

(2S)-*tert*.butoxycarbonylamino-cyclohexylacetic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (7.5 mg, 16 % yield), Purity by HPLC >95% $M+H^+$ 788.3.

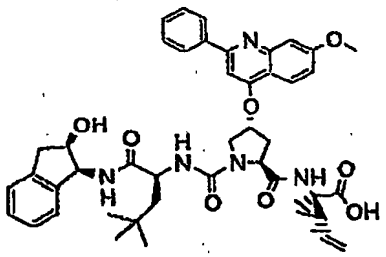
Example 88



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2,2-dimethyl-propylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (88).

(2S)-*tert*-butoxycarbonylamino-3,3-dimethylbutyric acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12 mg, 26 % yield), Purity by HPLC >95% $M+H^+$ 762.3.

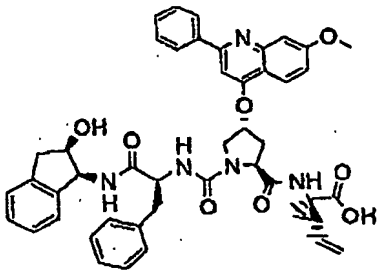
Example 89



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-3,3-dimethyl-butylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino)-2-vinyl-cyclopropanecarboxylic acid (89).

(2S)-*tert*-butoxycarbonylamino-4,4-dimethylpentanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (14.2 mg, 30 % yield), Purity by HPLC >95% $M+H^+$ 776.3.

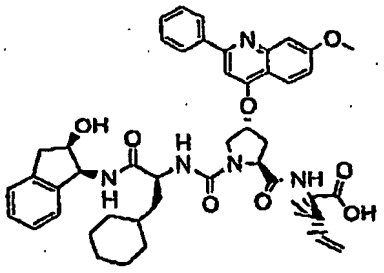
Example 90



(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-1-((1S, 2R)-2-Hydroxy-indan-1-ylcarbamoyl)-2-phenyl-etylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (90).

(2S)-*tert*-butoxycarbonylamino-3-phenylpropanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (2.4 mg, 5 % yield), Purity by HPLC >95% $M+H^+$ 796.2.

Example 91

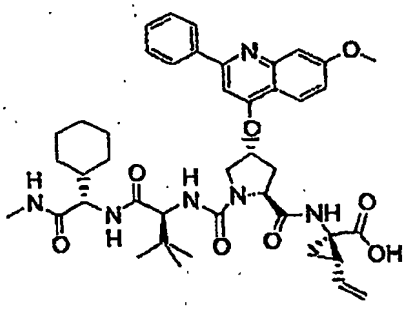


(1R, 2S)-1-{[(2S, 4R)-1-[(1S)-2-Cyclohexyl-1-((1S, 2R)-2-hydroxy-indan-1-ylcarbamoyl)-ethylcarbamoyl]-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (91).

(2S)-*tert*-Butoxycarbonylamino-3-cyclohexylpropanoic acid was attached to the resin as described for the preparation of compound 66 followed by reaction with (1S,2R)-

1-amino-2-indanol as described for the preparation of 67 and removal of the Boc group as described for 68. The afforded compound was then reacted with the chlorocarbamate achieved from 62 as described for the preparation of 63 which, after purification by HPLC, gave the title compound (12.3 mg, 26 % yield). Purity by HPLC >95% $M+H^+$ 802.3.

Example 92



(1R, 2S)-1-{[(2S, 4R)-1-{(1S)-1-[(S)-(Cyclohexyl-methylcarbamoyl-methyl)-carbamoyl]-2,2-dimethyl-propylcarbamoyl}-4-(7-methoxy-2-phenyl-quinolin-4-yloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid (92).

Compound 62 was treated as described for the preparation of 63 but with the use of 71 instead of 2-amino-*N*-(2-hydroxy-indan-1-yl)-3,3-dimethyl-butyramide followed by ester hydrolysis as described for the preparation of compound 64 which, after purification by HPLC, gave the title compound(8.6 mg, 18 % yield). Purity by HPLC >95%, $M+H^+$ 783.3.

Assays

The compounds of the invention are conveniently assayed for activity against the NS3 protease of flavivirus such as HCV using conventional in vitro (enzyme) assays or cell culture assays.

A useful assay is the Bartenshlager replicon assay disclosed in EP 1043399. An alternative replicon assay is described in WO 03064416.

A convenient enzyme assay involving the inhibition of full-length hepatitis C NS3 is essentially as described in Poliakov, 2002 Prot Expression & Purification 25 363 371. Briefly, the hydrolysis of a depsipeptide substrate, Ac-DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH_2 (AnaSpec, San José, USA), is measured spectrofluorometrically in the presence of a peptide cofactor, KKGSVVIVGRIVLSGK, as described by Landro, 1997 Biochem 36 9340-9348. The enzyme (1 nM) is incubated in a buffer such as 50 mM HEPES, pH 7.5, 10 mM DTT, 40% glycerol, 0.1% n-octyl-β-D-glucoside, with 25 μM cofactor and inhibitor at say 30 °C for 10 min, whereupon the reaction is initiated by addition of substrate, typically 0.5 μM substrate. Inhibitors are typically dissolved in DMSO, sonicated for 30 s and vortexed. The solutions are generally stored at –20°C between measurements.

An alternative enzyme assay is described in WO 0399316 and employs an HCV NS3/4A protease complex FRET peptide assay. The purpose of this in vitro assay is to measure the inhibition of HCV NS3 protease complexes, derived from the BMS, H77C or J416S strains, as described below, by compounds of the present invention. This assay provides an indication of how effective compounds of the present invention would be in inhibiting HCV proteolytic activity.

Serum is taken from an HCV-infected patient. An engineered full-length cDNA template of the HCV genome (BMS strain) was constructed from DNA fragments obtained by reverse transcription-PCR (RT-PCR) of serum RNA and using primers selected on the basis of homology between other genotype Ia strains. From the determination of the entire genome sequence, a genotype I a was assigned to the HCV isolate according to the classification of Simmonds et al. (See P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, J.Clin. Microbiol., 31(6), 1493-1503 (1993)). The amino acid sequence of the nonstructural region, NS2-5B, was shown to be >97% identical to HCV genotype

Ia (H77C) and 87% identical to genotype Ib (J4L6S). The infectious clones, H77C (I a genotype) and J4L6S (I b genotype) can be obtained from R. Purcell (NIH) and the sequences are published in Genbank (AAB67036, see Yanagi,M., Purcell,R.H., Emerson,S.U. and Bukh. Proc. Natl. Acad. Sci. U.S.A. 94 (16) 8738-8743 (1997); AF054247, see Yanagi,M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukhj, Virology 244 (1), 161 (1998)).

The BMS, H77C and J4L6S strains are used for production of recombinant NS3/4A protease complexes. DNA encoding the recombinant HCV NS3/4A protease complex (amino acids 1027 to 1711) for these strains were manipulated as described by P. Gallinari et al. (see Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. Biochemistry. 38(17):562032, (1999)). Briefly, a three-lysine solubilizing tail was added at the 3'-end of the 3 0 NS4A coding region. The cysteine in the P1 position of the NS4A-NS4B cleavage site (amino acid 1711) was changed to a glycine to avoid the proteolytic cleavage of the lysine tag. Furthermore, a cysteine to serine mutation can be introduced by PCR at amino acid position 1454 to prevent the autolytic cleavage in the NS3 helicase domain. The variant DNA fragment can be cloned in the pET21b bacterial expression vector (Novagen) and the NS3/4A complex can be expressed in Escherichia coli strain BL21 (DE3) (Invitrogen) following the protocol described by P. Gallinari et al. (see Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., J Virol. 72(8):6758-69 (1998)) with modifications. Briefly, NS3/4A expression can be induced with 0.5mM Isopropyl beta-D thiogalactopyranoside (IPTG) for 22hr at 20'C. A typical fermentation (I0 l) yields approximately 80g of wet cell paste. The cells are resuspended in lysis buffer (IO mL/g) consisting of 25mM N-(2Hydroxyethyl)Piperazine-N'-(2-Ethane Sulfonic acid) (HEPES), pH7.5, 20% glycerol, 5OOmM Sodium Chloride (NaCl), 0.5% Triton-X100, I ug/ml lysozyme, 5mM Magnesium Chloride (MgCl2), I ug/ml Dnasel, 5mM beta-Mercaptoethanol (BME), Protease inhibitor - Ethylenediamine Tetraacetic acid (EDTA) free (Roche), homogenized and incubated for 20 mins at VC. The homogenate is sonicated and clarified by ultra-centrifugation at 235000 g for 1 hr at 4'C.

Imidazole is added to the supernatant to a final concentration of 15mM and the pH adjusted to 8. The crude protein extract is loaded on a Nickel Nitrilotriacetic acid (Ni-NTA) column pre-equilibrated with buffer B (25n-tM 2 0 HEPES, pH8 20% glycerol, 5OOmM NaCl, 0.5% Triton-XlOO, 15mM imidazole, 5mM BME). The sample is loaded at a flow rate of lmL/min. The column is washed with 15 column volumes of buffer C (same as buffer B except with 0.2% Triton-X100). The protein is eluted with 5 column volumes of buffer D (same as buffer C except with 200mM imidazole).

NS3/4A protease complex-containing fractions are pooled and loaded on a desalting column Superdex-S200 pre-equilibrated with buffer D (25MM HEPES, pH7.5, 20% glycerol, 3OOmM NaCl, 0.2% Triton-XlOO, lOmM BME). Sample is loaded at a flow rate of lmUmin. NS3/4A protease complex3 0 containing fractions are pooled and concentrated to approximately 0.5mg/ml. The purity of the NS3/4A protease complexes, derived from the BMS, H77C and J4L6S strains, are typically judged to be greater than 90% by SDS-PAGE and mass spectrometry analyses.

The enzyme is generally stored at -80'C, thawed on ice and diluted prior to use in assay buffer. The substrate used for the NS3/4A protease assay, is conveniently RET S 1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991)(FRET peptide), described by Taliani et al. in Anal. Biochem. 240(2):6067 (1996). The sequence of this peptide is loosely based on the NS4A/NS4B natural cleavage site except there is an ester linkage rather than an amide bond at the cleavage site. The peptide substrate is incubated with one of the three recombinant NS3/4A complexes, in the absence or presence of a compound of the present invention, and the formation of fluorescent reaction product was followed in real time using a Cytofluor Series 4000. Useful reagents are as follow: HEPES and Glycerol (Ultrapure) can be obtained from GIBCO-BRL. Dimethyl Sulfoxide (DMSO) is obtained from Sigma. Beta-Mercaptoethanol is obtained from Bio Rad.

Assay buffer: 50m.M HEPES, pH7.5; 0. 15M NaCl; 0. I% Triton; 15 % Glycerol; 10mM BME. Substrate: 2 uM final concentration (from a 2mM stock 2 0 solution in DMSO stored at -20'C). HCV NS3/4A type Ia (Ib), 2-3 nM final concentration (from a 5uM stock solution in 25mM HEPES, pH7.5, 20% glycerol, 300m.M NaCl, 0.2% Triton-X100, 10mM BME). For compounds with potencies approaching the assay limit, the assay can be made more sensitive by adding 50 ug/ml BSA to the assay buffer and/or reducing the end protease concentration to 300 pM.

The assay is conveniently performed in a 96-well polystyrene black plate from Falcon. Each well contains 25ul NS3/4A protease complex in assay buffer, 50ul of a compound of the present invention in 10% DMSO/assay buffer and 25ul substrate in assay buffer. A control (no compound) is also prepared on the same assay plate. The enzyme complex is mixed with compound or control solution, typically for 1 min before initiating the enzymatic reaction by the addition of substrate. The assay plate is generally read immediately using a spectrophotometer such as a Cytofluor Series 4000 (Perspective Biosysterns). The instrument is conveniently set to read an emission of 340nm and excitation of 490nm at 25'C. Reactions are generally followed for approximately 15 minutes.

The percent inhibition can be calculated with the following equation.

$$100.- [(dF_{inh}/dF_{con})X100]$$

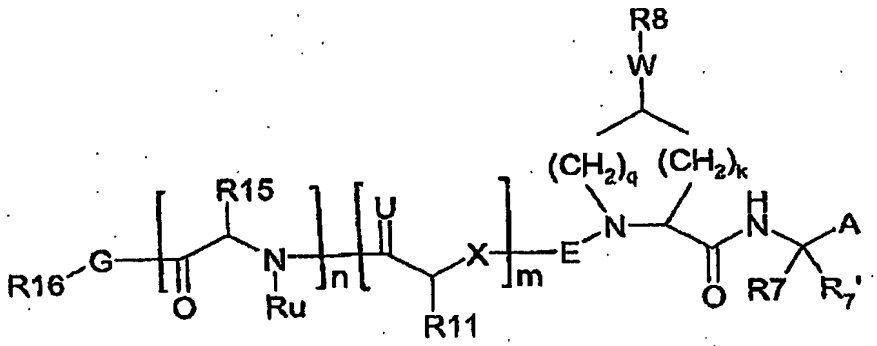
where dF is the change in fluorescence over the linear range of the curve. A nonlinear curve fit is applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) is calculated by the use software such as Excel XI-fit software using the equation:

$$y=A+((B-A)/(1+((C/x)^D))).$$

Various compounds of the invention exemplified above displayed IC_{50}s in the range 1nM to 6.9 micromolar and ED_{50}s in the sub-micromolar to micromolar range.

Claims

1. A compound of the formula I:



wherein

A is $COOR^1$, $CONHSO_2R^2$, $CONHR^3$, or $CR^4R^{4'}$ wherein;

R^1 is hydrogen, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^2 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^3 is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, -OC_1-C_6alkyl, -OC_0-C_3alkylcarbocyclyl, -OC_0-C_3alkylheterocyclyl;

R^4 is =O, halo, amino, or OH;

$R^{4'}$ is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl; wherein

R^2, R^3, and R4' are each optionally substituted with from 1 to 3 times with halo, oxo, nitrile, azido, nitro, C_1-C_8alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p$$R_b$, Y-S(=O)$_p$$R_b$, Y-S(=O)$_pNRaR_b$, Y-C(=O)O$R_b$, Y-NRaC(=O)O$R_b$;

where Y is a bond or C_1-C_3 alkyl;

Ra is H or C_1-C_3 alkyl;

Rb is H or C_1-C_8 alkyl;

p is 1 or 2;

R^7 is C_1-C_6alkyl, C_1-C_3alkyl C_3-C_7cycloalkyl, or C_2-C_6alkenyl, any of which is optionally substituted with 1-3 halo atoms, amino or –SH;

$R^{7'}$ is H or taken together with R^7 to form a C_3-C_6 cycloalkyl ring optionally substituted with $R^{7'a}$ wherein;

$R^{7'a}$ is C_1-C_6 alkyl, C_3-C_5cycloalkyl, C_2-C_6 alkenyl or J; any of which may be optionally substituted with halo;

q is 0 to 3 and k is 0 to 3; where $q+k \geq 1$;

W is $-CH_2-$, -O-, -OC(=O)NH-, -OC(=O)-, -S-, –NH-, $-NR^{8'}$, $-NHSO_2-$ or -NHC(=O)-;

R^8 is a ring system containing 1 or 2 saturated or unsaturated rings each of which has 4-7 ring atoms and 0 to 2 hetero atoms selected from S, O and N, the ring system being optionally spaced from W by a C_1-C_3 alkyl group; or R^8 is C_1-C_6 alkyl, any of which R^8 groups can be optionally mono, di, or tri substituted with R^9, wherein

R^9 is independently halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p R_b$, Y-S(=O)$_p R_b$, Y-S(=O)$_p$NRaR_b, Y-C(=O)OR_b, Y-NRaC(=O)OR_b; wherein the carbocyclyl or heterocyclyl is optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di- substituted with C_1-C_6-alkyl, sulfonyl, (C_1-C_3 alkyl)sulfonyl, NO_2, OH, SH, halo, haloalkyl, carboxyl, amide, (C_1-C_3alkyl)amide, or heteroaryl optionally substituted with C_1-C_6alkyl;

$R^{8'}$ is H, C_1-C_3 alkyl;

E is -C(=O)-, -C(=S)-, $-S(=O)_2-$, -S=O-, -C=N-Rf;

Rf is H, -CN, -C(=O)NRaRb; -C(=O)C_1-C_3 alkyl

X is –NRx- where Rx is H, or C_1-C_5alkyl; or in the case where where E is –(C=O)- X can also be –O-;

R^{11} is H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p R_b$, Y-S(=O)$_p R_b$, Y-S(=O)$_p$NRaR_b, Y-C(=O)OR_b, Y-NRaC(=O)OR_b;

when $R^{7'}$ taken together with R^7 forms a C_3-C_6 cycloalkyl, then one of Rx or R^{11} can also be J;

J is a 3 to 10-membered saturated or unsaturated alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rx or R^{11} to form a macrocycle, which chain is optionally interrupted by one to three heteroatoms independently selected from: -O-, -S- or -NR^{12}- wherein 0 to 3 carbon atoms in the chain are optionally substituted with R^{14};

wherein;

R^{12} is H, C_1-C_6 alkyl, C_3-C_6cycloalkyl, or COR^{13};

R^{13} is C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl;

R^{14} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, hydroxy, halo, amino, oxo, thio, or C_1-C_6 thioalkyl;

Ru and Rz are independently H or C_1-C_3 alkyl;

m is 0 or 1; n is 0 or 1;

U is =O or is absent;

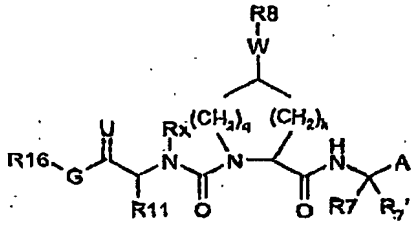
R^{15} is H, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylheteroaryl, C_0-C_3alkylcycloC_3-C_6alkyl, NH_2CO-, Y-NRaRb, Y-O-R_b, Y-C(=O)R_b, Y-(C=O)NRaR_b, Y-NRaC(=O)R_b, Y-NHS$O_p$$R_b$, Y-S(=O)$_p$$R_b$, Y-S(=O)$_pNRaR_b$, Y-C(=O)O$R_b$, Y-NRaC(=O)O$R_b$;

G is –O-, -NRy- or –NHNH- where Ry is H or C_1-C_3 alkyl;

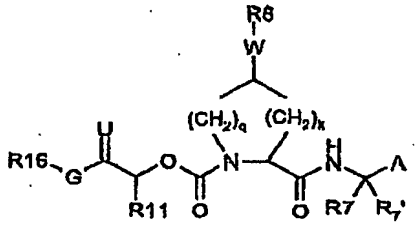
R^{16} is H; or C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, any of which can be substituted with halo, oxo, nitrile, azido, nitro, C_1-C_6alkyl, C_0-C_3alkylcarbocyclyl, C_0-C_3alkylheterocyclyl, NH_2CO-, Y-NRaRb, Y-O-Rb, Y-C(=O)Rb, Y-(C=O)NRaRb, Y-NRaC(=O)Rb, Y-NHSO_pRb, Y-S(=O)$_p$Rb, Y-S(=O)$_p$NRaRb, Y-C(=O)ORb, Y-NRaC(=O)ORb;

or a pharmaceutically acceptable salt or prodrug thereof.

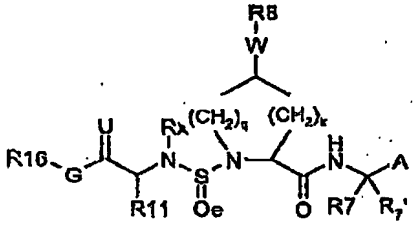
2. A compound according to claim 1 with the formula IIa, IIb or IIc



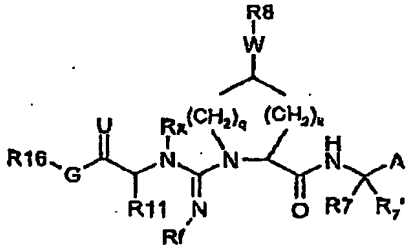
IIa



IIb



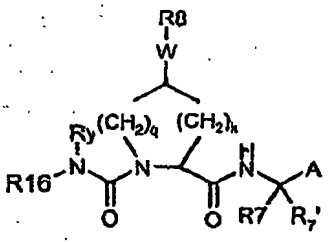
IIc



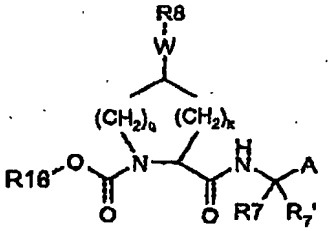
IIaa

where e is 1 or 2.

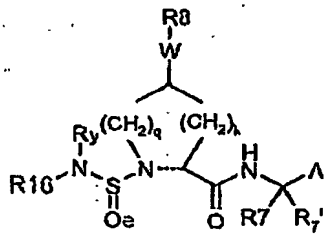
3. A compound according to claim 1 with the formula IIIa, IIIb or IIIc



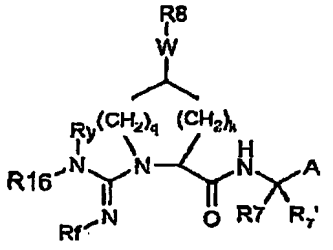
IIIa



IIIb



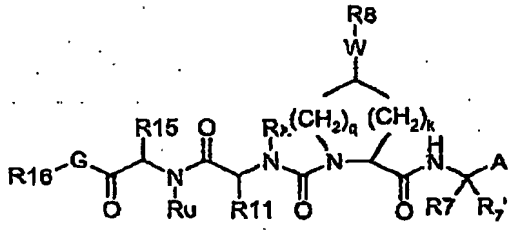
IIIc

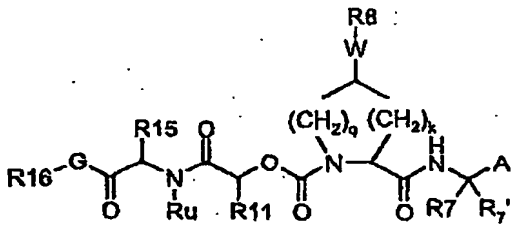


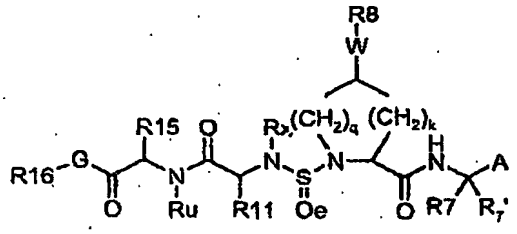
IIIaa

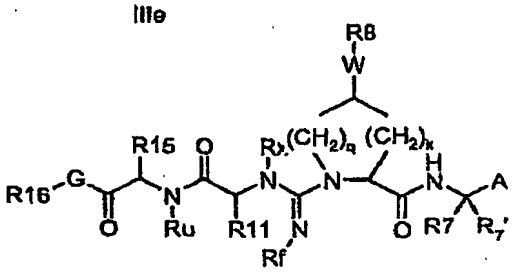
where e is 0 to 2.

4. A compound according to claim 1, with the formula IIId, IIIe or IIIf


IIId

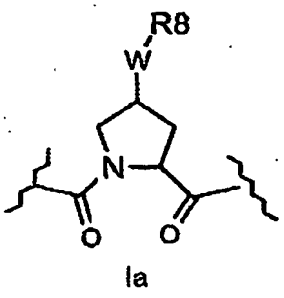

IIIe

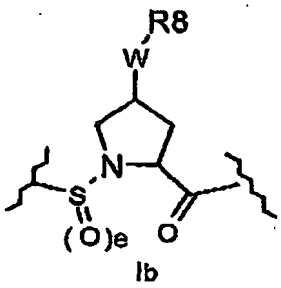

IIIf

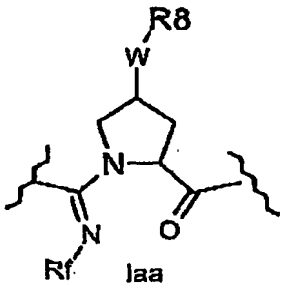

IIIfa

5. A compound according any preceding claim, wherein X is –NRx-.

6. A compound according to any preceding claim with the partial structure Ia or Ib:


Ia

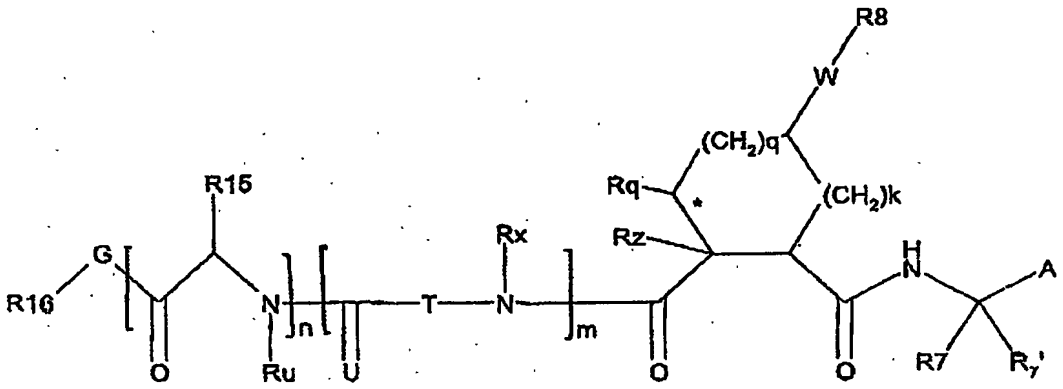

Ib


Iaa

where e is 1 or 2

7 A compound according to any preceding claim, wherein E is –C(=O)- or –C=NRf.

8. A compound with the formula VI



VI

wherein

R^7, $R^{7'}$, R^8, R^{11}, R^{15}, R^{16}, Rx, Ru, A, G, k, m, n, U are as defined in claim 1;

q' is 0 or 1;

Rz is H, or together with the asterisked carbon forms an olefinic bond;

Rq is H or C_1-C_4-alkyl;

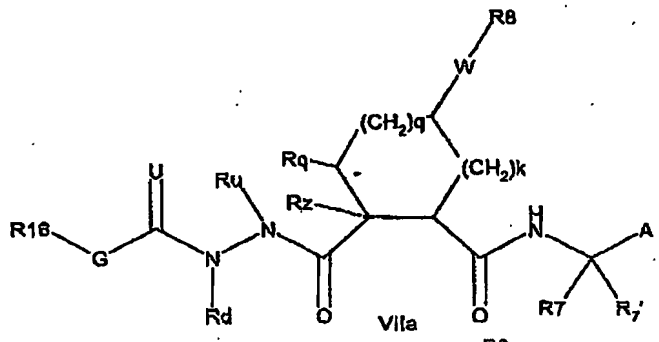
T is $-CHR^{11}-$ or $-NRd-$, where Rd is H or C_1-C_3alkyl;

in the case where R^7 taken together with $R^{7'}$ forms a C_3-C_6 cycloalkyl, one of Rx, Rd or R^{11} can be J;

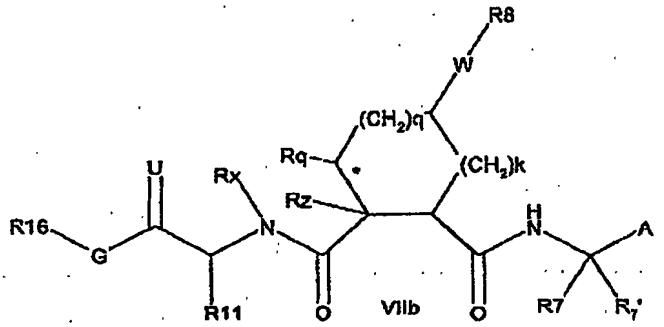
J is a 5 to 10 membered saturated or unsaturated alkylene chain extending from the $R^7/R^{7'}$ cycloalkyl to Rx, Rd or R^{11} to form a macrocycle, which chain is otherwise as defined in claim 1;

and pharmaceutically acceptable salts and prodrugs thereof

9. A compound according to claim 8 with the formula VIIa or VIIb:

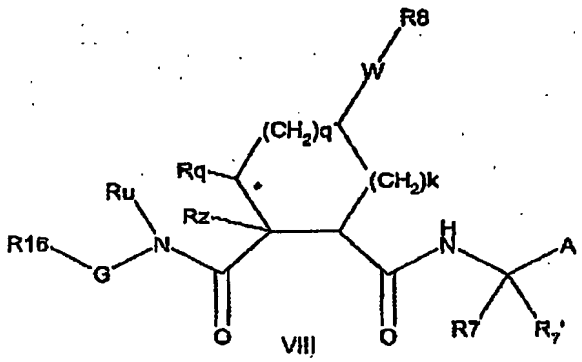


VIIa



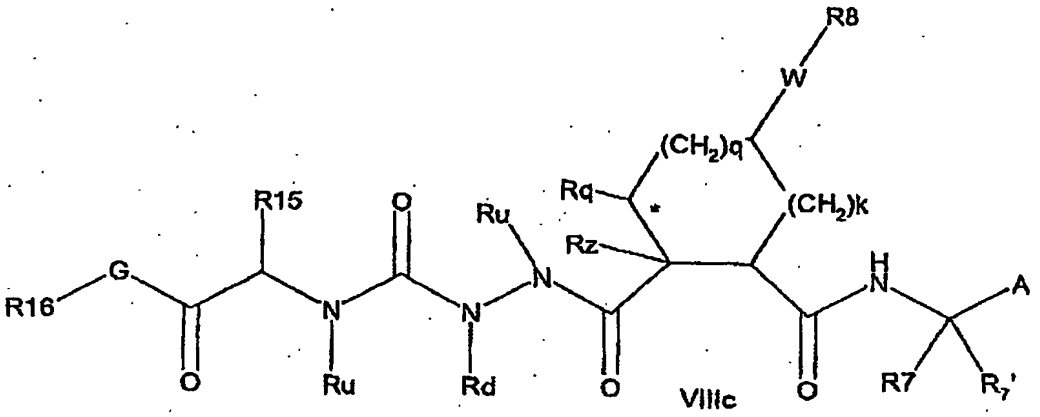
VIIb

10. A compound according to claim 8 with the formula VIII.

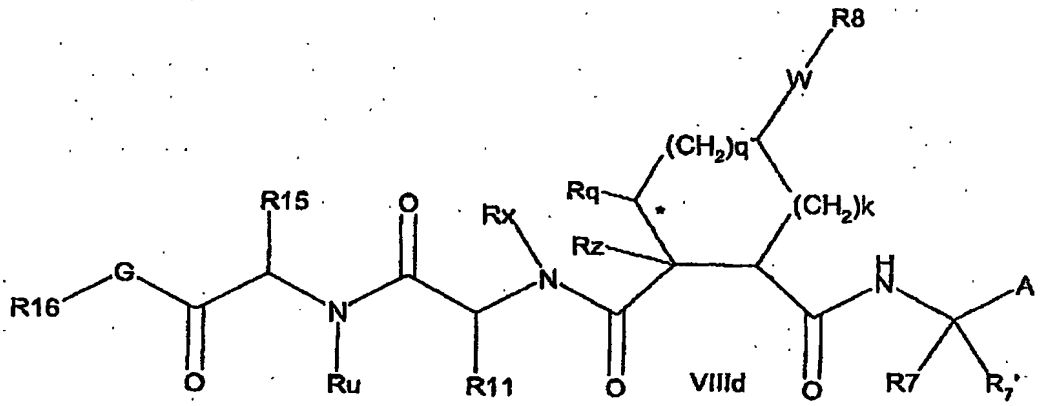


VIII

11. A compound according to claim 8 with the structure VIIc or VIId



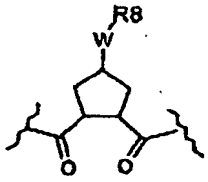
VIIIc



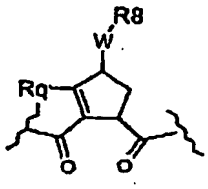
VIIId

12. A compound according to any of claims 8 to 11, wherein Rz is H.

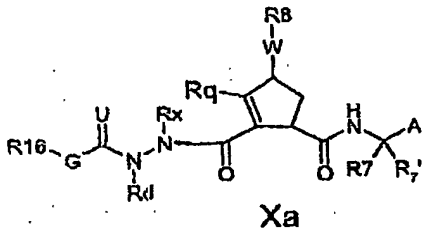
13. A compound according to any of claims 8 to 12 with the partial structure:



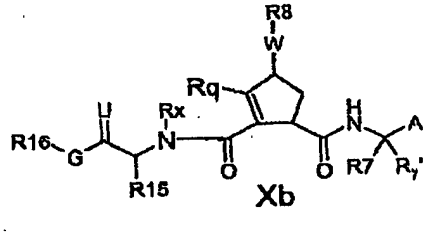
14. A compound according to any of claims 8 to 12 with the partial structure



15. A compound according to claim 14, with the formula Xa or Xb:

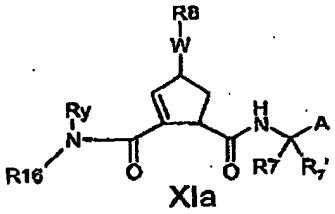


Xa



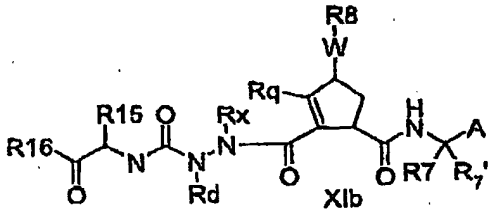
Xb

16. A compound according to claim 14, with the formula XIa:

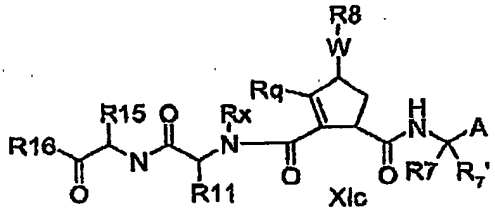


XIa

17. A compound according to claim 14, with the formula XIb or XIc



XIb



XIc

18. A compound according to any of claims 8 to 17, where Rq is H or methyl

19. A compound according to any preceding claim wherein $R^{7'}$ is H and R^7 is n-ethyl, n-propyl, cyclopropylmethyl, cyclobutylmethyl, 2,2-difluoroethyl, or mercaptomethyl.

20. A compound according to claim 19, wherein R^7 is n-propyl or 2,2-difluoroethyl.

21. A compound according to any of claims 1 to 18 wherein R^7 and $R^{7'}$ together define a spiro-cyclopropyl or spiro-cyclobutyl ring, both optionally mono or di-substituted with R^{7a} wherein;

R^{7a} is C_1-C_6 alkyl, C3-C5cycloalkyl, or C_2-C_6 alkenyl, any of which is optionally substituted with halo or J.

22. A compound according to claim 21 wherein the ring is a spiro-cyclopropyl ring substituted with R^{7a} wherein;

R^{7a} is ethyl, vinyl, cyclopropyl, 1- or 2-bromoethyl, 1-or 2-fluoroethyl, 2-bromovinyl or 2-fluorethyl.

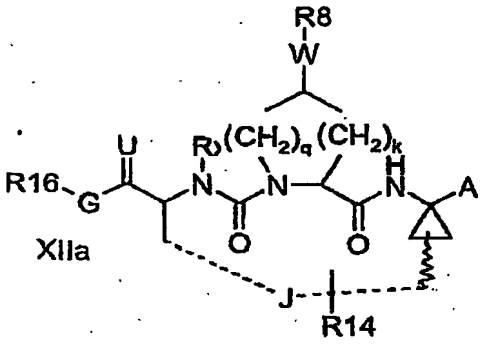
23 A compound according to claim 21, wherein J is a 3 to 8-membered saturated or unsaturated alkylene chain optionally containing one to two heteroatoms independently selected from: -O-, -S- or $-NR^{12}-$, wherein R^{12} is H, C_1-C_6 alkyl, such as methyl, or $-C(=O)C_1$-C_6 alkyl, such as acetyl.

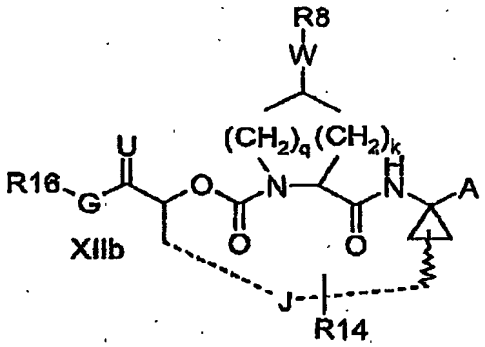
24. A compound according to claim 24 wherein J is a 5 to 8-membered saturated or unsaturated, all carbon alkylene chain.

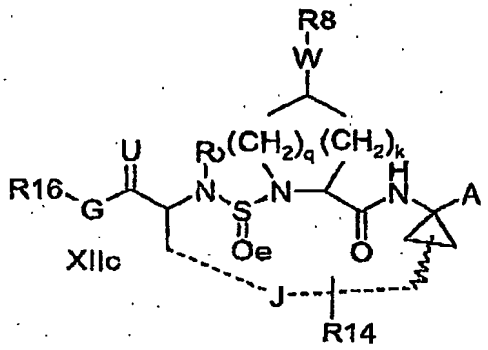
25. A compound according to claim 23 or 24 wherein J is saturated or mono-unsaturated.

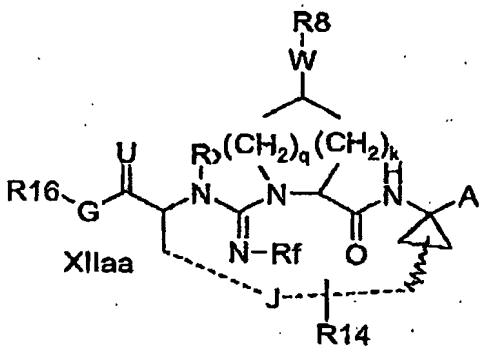
26. A compound according to claim 23, 24 or 25, wherein J is substituted with R^{14}, wherein R^{14} is H or C_1-C_6alkyl.

27. A compound according to claims 23-26 with the formula XIIa, XIIb or XIIc



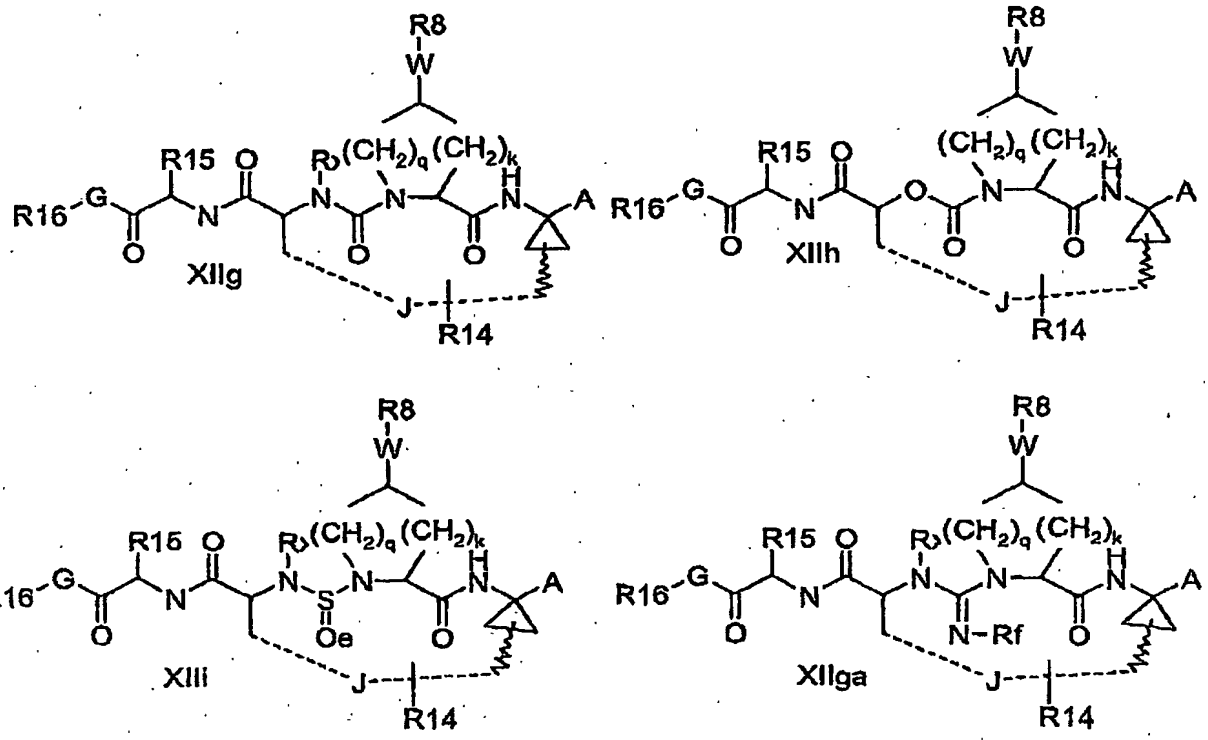




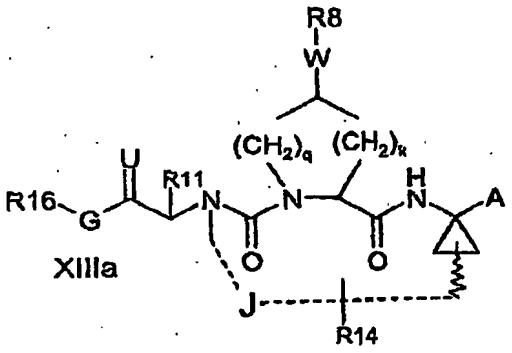


where e is 1 or 2.

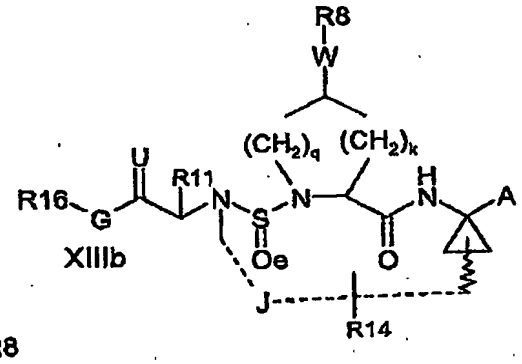
28. A compound according to claims 23 to 26 with the structure XIIg, XIIga, XIIh or XIIi.



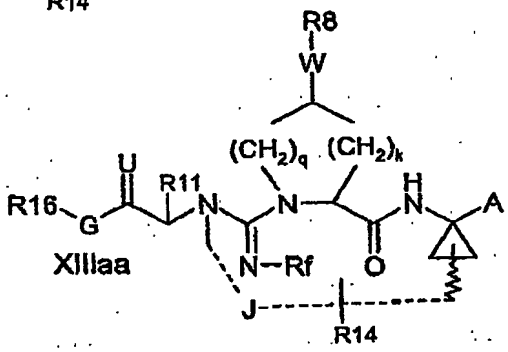
29. A compound according to claims 23-26 with the formula XIIIa, XIIIaa or XIIIb



XIIIa

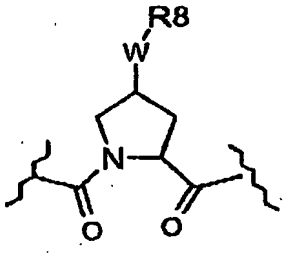


XIIIb

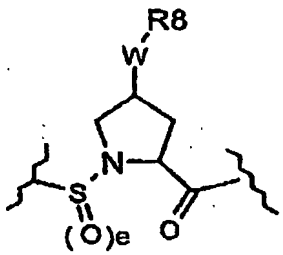


XIIIaa

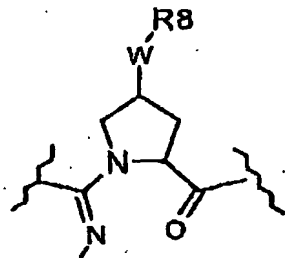
30. A compound according to claim 27, 28 or 29 with the partial structure



Ia

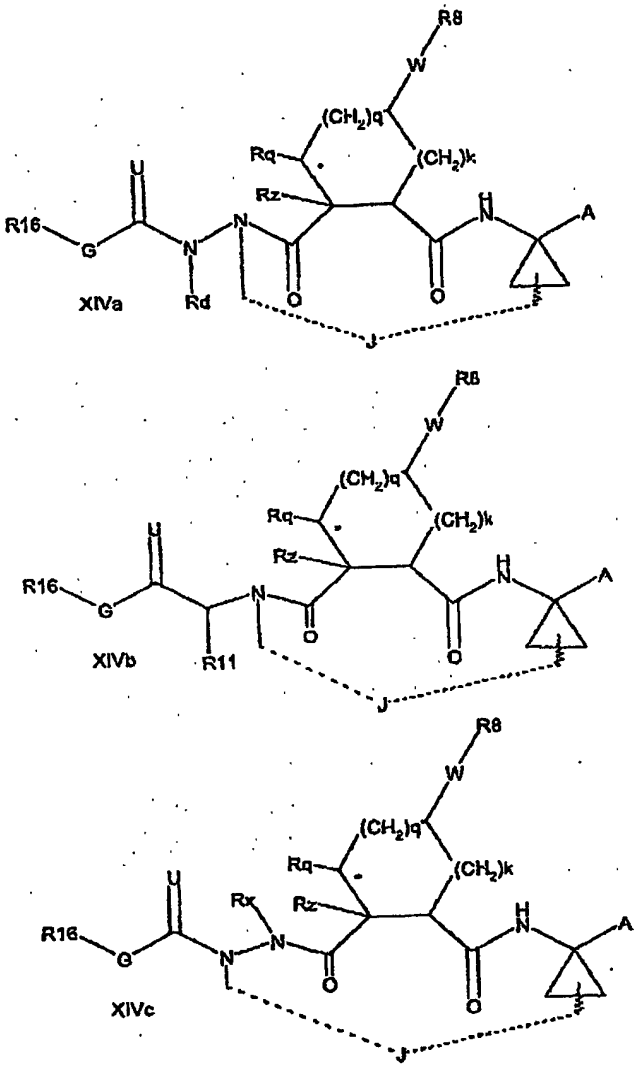


Ib

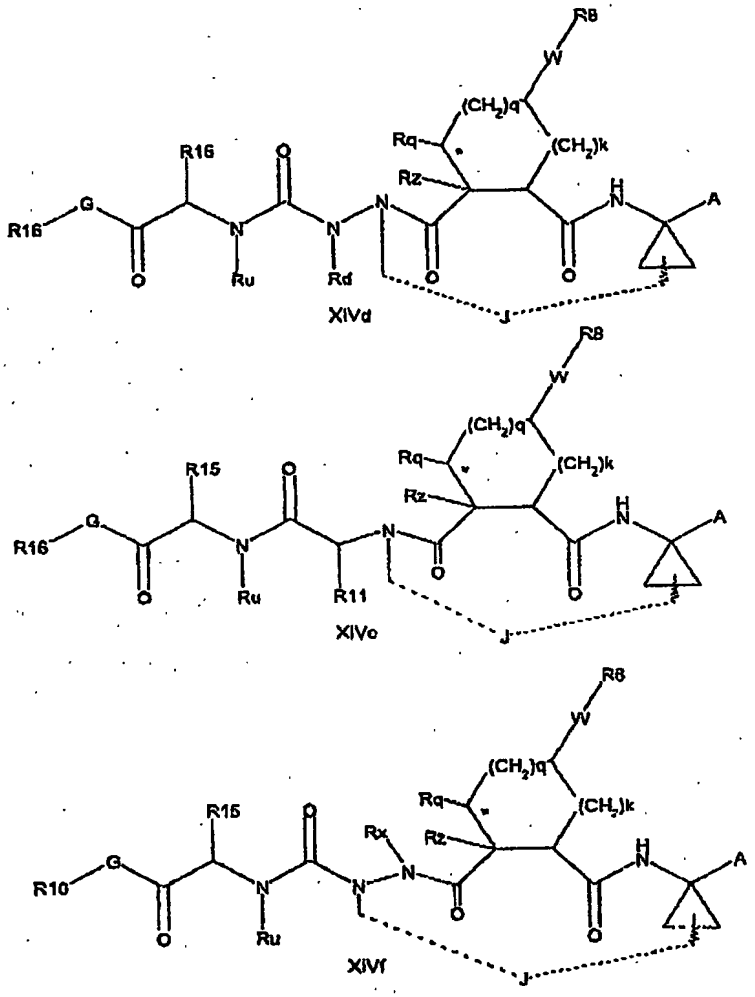


Iaa

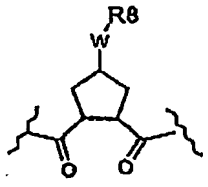
31. A compound according to claims 23 to 26 with the formula XIVa, XIVb or XIVc



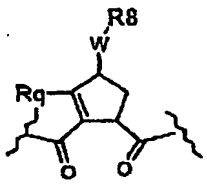
33. A compound according to claims 23 to 26 with the formula XIVd, XIVe or XIVf:



33. A compound according to claim 31 or 32 with the partial structure:



34. A compound according to claim 32 or 33 with the partial structure



35. A compound according to claim 34, wherein Rq is methyl or H.

36. A compound according to any preceding claim, wherein A is $-CR^4R^{4'}$

37. A compound according to claim 36, wherein R^4 is C_1-C_6alkyl.

38. A compound according to claim 35, wherein R^4 is C_1-C_3alkylaryl or C_1-C_3alkylheteroaryl.

39. A compound according to claim 37 or 38, wherein the alkyl moiety of R^4 is C_1 – C_3 alkanyl or C_2-C_3 alkenyl.

40. A compound according to claim 41 or 42, wherein the aryl moiety of R^4 is optionally substituted phenyl.

41. A compound according to claim 38 or 39, wherein the heteroaryl moiety of R^4 is optionally substituted benzothiazole.

42. A compound according to claims 36 to 41, wherein $R^{4'}$ is $-NH_2$, fluoro or chloro.

43. A compound according to claims 36 to 41, wherein $R^{4'}$ is –OH.

44. A compound according to claims 35 to 41, wherein $R^{4'}$ is =O.

45. A compound according to claims 1 to 35, wherein A is $CONHR^3$.

46. A compound according to claim 45, wherein R^3 is optionally substituted C_0-C_3alkylaryl, C_0-C_3alkylhetroaryl, OC_0-C_3alkylaryl or OC_0-C_3alkylhetroaryl.

47. A compound according to claim 46, wherein R^3 is optionally substituted C_0-C_3alkylaryl or C_0-C_3alkylhetroaryl.

48. A compound according to claims 1 to 35, wherein A is $CONHSO_2R^2$.

49. A compound according to claim 48, wherein R^2 is optionally substituted C_1-C_6 alkyl, preferably methyl.

50. A compound according to claim 48, wherein R^2 is optionally substituted C_3-C_7cycloalkyl, preferably cyclopropyl.

51. A compound according to claim 48 wherein R^2 is optionally substituted C_0-C_6alkylaryl, preferably optionally substituted phenyl.

52. A compound according to claims 1 to 35, wherein A is $COOR^1$.

53. A compound according to claim 52, wherein R^1 is H or C_1-C_6 alkyl

54 A compound according to claim 51 wherein R^1 is hydrogen, methyl, ethyl, or tert-butyl.

55 A compound according to any preceding claim, wherein W is -OC(=O)NH-, -OC(=O)-, -NH-, $-NR^{6'}$-, $-NHS(O)_2$-or -NHC(=O)-.

56 A compound according to claim 55 wherein W is –OC(=O)NH- or –NH-

57 A compound according to claim 55 or 56 wherein R^8 is optionally substituted C_0-C_3-alkylcarbocyclyl or C_0-C_3-alkylheterocyclyl.

58 A compound according to claims 1 to 54 wherein W is -S- or preferably –O-.

59 A compound according to claim 58 wherein R^8 is C_0-C_3alkylaryl, or C_0-C_3alkylhetroaryl either of which is optionally mono, di, or tri substituted with R^9, wherein;

R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, NO_2, OH, halo, trifluoromethyl, amino or amido optionally mono- or di-substituted with C_1-C_6alkyl, C_0-C_3alkylaryl, C_0-C_3alkylhetroaryl, carboxyl, aryl or heteroaryl being optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, C_1-C_3 alkyl amide), sulfonylC_1-C_3alkyl, NO_2, OH, halo, trifluoromethyl, carboxyl, or hetroaryl.

60 A compound according to claim 59 wherein R^9 is C_1-C_6 alkyl, C_1-C_6alkoxy, amino, di-(C_1-C_3 alkyl)amino, C_1-C_3alkylamide, aryl or hetroaryl, the aryl or hetroaryl being optionally substituted with R^{10}; wherein

R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino, mono- or di-C_1-C_3 alkylamino, amido, C_1-C_3 alkylamide, halo, trifluoromethyl, or hetroaryl.

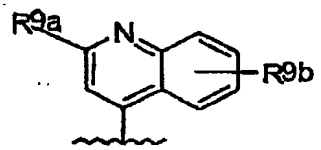
61 A compound according to claim 60, wherein, R^{10} is C_1-C_6alkyl, C_1-C_6alkoxy, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3-alkylamide, halo, or hetroaryl.

62. A compound according to any preceding claim wherein R^{10} is methyl, ethyl, isopropyl , tert-butyl, methoxy, chloro, amino optionally mono- or di substituted with C_1-C_3 alkyl, amido, C_1-C_3alkylamide, or C_1-C_3alkyl thiazole.

63 A compound according to claims 59 to 62, wherein R^8 is 1-naphthlmethyl, 2-naphtylmethyl, benzyl, 1-naphthyl, 2-naphthyl, or quinolinyl unsubstituted , mono, or disubstituted with R^9 as defined.

64 A compound according to claim 63 wherein R^8 is 1-naphthylmethyl, or quinolinyl unsubstituted , mono, or disubstituted with R^9 as defined.

65 A compound according to claim 63 wherein R^8 is:



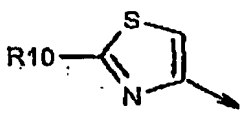
wherein R^{9a} is C_1-C_6 alkyl; C_1-C_6alkoxy; thioC_1-C_3alkyl; amino optionally substituted with C_1-C_6alkyl; C_0-C_3alkylaryl; or C_0-C_3 alkylheteroaryl, C_0-C_3 alkylheterocyclyl, said aryl, heteroaryl or heterocycle being optionally substituted with R^{10} wherein

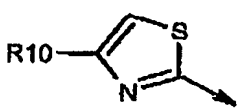
R^{10} is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6alkoxy, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, C_1-C_3alkyl amide, heteroaryl or heterocyclyl; and

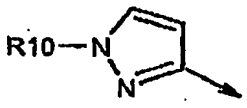
R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3alkyl)amino, (C_1-C_3alkyl) amide, NO_2, OH, halo, trifluoromethyl, carboxyl.

66 A compound according to claim 63, wherein R^{9a} is aryl or heteroaryl, all optionally substituted with R^{10} as defined.

67 A compound according to 66, wherein R^{9a} is selected from the group consisted of :



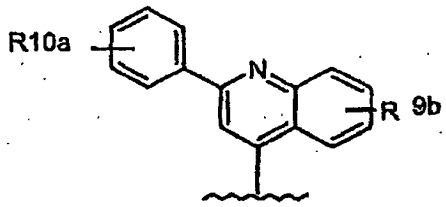




wherein R^{10} is H, C_1-C_6alkyl, or C_0-C_3alkyl-C_3-C_6cycloalkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3alkyl)amide, heteroaryl or heterocyclyl.

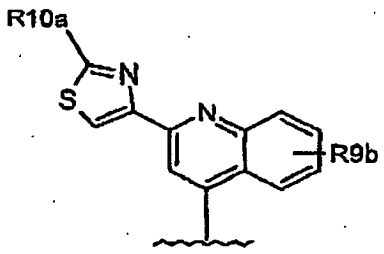
68. A compound according to claim 65, wherein R^{9a} is phenyl

69. A compound according to claim 68, wherein R^8 is:



wherein R^{10a} is H, C_1-C_6alkyl; C_1-C_6alkoxy; or halo; and R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3alkyl)amino, (C_1-C_3alkyl)amide, NO_2, OH, halo, trifluoromethyl, carboxyl.

69. A compound according to claim 65, wherein R^8 is:



wherein R^{10a} is H, C_1-C_6alkyl, or C_0-C_3alkyl-C_3-C_6cycloalkyl, amino optionally mono- or di-substituted with C_1-C_6alkyl, amido, (C_1-C_3 alkyl)amide, heteroaryl or heterocyclyl; and R^{9b} is C_1-C_6 alkyl, C_1-C_6-alkoxy, amino, di(C_1-C_3 alkyl)amino, (C_1-C_3 alkyl)amide, NO_2, OH, halo, trifluoromethyl, or carboxyl.

70. A compound according to any claim 65-70, wherein R^{9b} is C_1-C_6-alkoxy, preferably methoxy.

71. A compound according to any preceding claim, wherein Rx is methyl or preferably H.

72. A compound according to any preceding claim, wherein R^{11} is C_1-C_6alkyl, C_0-C_3 alkylC_3-C_7 cycloalkylyl, C_0-C_3alkylaryl or C_0-C_3 alkylheteroaryl, any of which is optionally substituted with hydroxy, halo, amino, C_1-C_6alkoxy, C_1-C_6thioalkyl, $COOR^{14}$, carboxyl, (C_1-C_6alkoxy)carbonyl, aryl, heteroaryl or heterocyclyl;

73 A compound according to claim 72, wherein the substituent is hydroxy or $COOR^{14}$.

74. A compound according to claim 73, wherein R^{11} is tert-butyl, iso-butyl, cyclohexyl, phenylethyl, 2,2-dimetyl-propyl, cyclohexylmethyl, phenylmethyl, 2-pyridylmethyl, 4-hydroxy-phenylmethyl, or carboxylpropyl.

75. A compound according to claim 74, wherein R^{11} is tert-butyl, iso-butyl, or cyclohexyl.

76. A compound according to claim 1 or 8, wherein Ru is methyl or preferably H.

77. A compound according to any preceding claim, wherein R^{15} is optionally substituted C_1-C_6alkyl, C_3-C_7cycloalkyl, C_0-C_3alkylC_3-C_7cycloalkyl.

78. A compound according to claim 77, wherein R^{15} is cyclohexyl, cyclohexylmethyl, tert-butyl iso-propyl, or iso-butyl.

79. A compound according to claim 1 or 8, wherein m is zero and T is absent.

80. A compound according to any preceding claim, wherein G is –NRy- .

81. A compound according to claim 80, wherein Ry is methyl or preferably H.

82. A compound according to any of claims 1 to 79, wherein G is O.

83. A compound according to any preceding claim, wherein R^{16} is C_1-C_6alkyl, C_0-C_3alkylheterocyclyl, C_0-C_3alkylcarbocyclyl, any of which is optionally substituted with hydroxy, halo, amino, or C_1-C_6alkoxy.

84. A compound according to claim 83, wherein R^{16} is methyl.

85. A compound according to claim 83, wherein R^{16} is 2-indanol, indanyl, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, cyclohexylmethyl, 2,3-methylenedioxybenzyl, cyclohexyl, benzyl, 2-pyridylmetyl, cyclobutyl, iso-butyl, n-propyl, or 4-methoxyphenylethyl.

86. A compound according to claim 83, wherein R^{16} is 2-indanol, indan, 2-hydroxy-1-phenyl-ethyl, 2-thiophenemethyl, 2,3-methylenedioxybenzyl, or cyclohexylmethyl.

87. A pharmaceutical composition comprising a compound as defined in any preceding claim and a pharmaceutically acceptable carrier therefore.

88. A pharmaceutical composition according to claim 87, further comprising an additional HCV antiviral, selected from nucleoside analogue polymerase inhibitors, protease inhibitors, ribavirin and interferon.

89. Use of a compound as defined in any of claims 1-86 in the manufacture of a medicament for the prophylaxis or treatment of flavivirus infections, including HCV.

Abstract of the Disclosure

Peptidomimetic compounds are described which inhibit the NS3 protease of the hepatitis C virus (HCV). The compounds comprise a novel linkage between a carbocyclic or heterocyclic P2 unit and those portions of the inhibitor more distal to the cleavage site, which linkage which reverses the orientation of peptidic bonds on the distal side relative to those proximal to the cleavage site.

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